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Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children (Review)

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TABLE OF CONTENTS

[Intervention Review]

Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children

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ABSTRACT

Background

Respiratory viruses are the leading cause of lower respiratory tract infection (LRTI) and hospitalisation in infants and young children. Respiratory syncytial virus (RSV) is the main infectious agent in this population. Palivizumab is administered intramuscularly every month during five months in the first RSV season to prevent serious RSV LRTI in children. Given its high cost, it is essential to know if palivizumab continues to be effective in preventing severe RSV disease in children.

Objectives

To assess the effects of palivizumab for preventing severe RSV infection in children.

Search methods

We searched CENTRAL, MEDLINE, three other databases and two trials registers to 14 October 2021, together with reference checking, citation searching and contact with study authors to identify additional studies. We searched Embase to October 2020, as we did not have access to this database for 2021.

Selection criteria

We included randomised controlled trials (RCTs), including cluster-RCTs, comparing palivizumab given at a dose of 15 mg/kg once a month (maximum five doses) with placebo, no intervention or standard care in children 0 to 24 months of age from both genders, regardless of RSV infection history.

Data collection and analysis

We used Cochrane's Screen4Me workflow to help assess the search results. Two review authors screened studies for selection, assessed risk of bias and extracted data. We used standard Cochrane methods. We used GRADE to assess the certainty of the evidence. The primary outcomes were hospitalisation due to RSV infection, all-cause mortality and adverse events. Secondary outcomes were hospitalisation due to respiratory-related illness, length of hospital stay, RSV infection, number of wheezing days, days of supplemental oxygen, intensive care unit length of stay and mechanical ventilation days.

Main results

We included five studies with a total of 3343 participants. All studies were parallel RCTs, assessing the effects of 15 mg/kg of palivizumab every month up to five months compared to placebo or no intervention in an outpatient setting, although one study also included hospitalised infants. Most of the included studies were conducted in children with a high risk of RSV infection due to comorbidities like bronchopulmonary dysplasia and congenital heart disease. The risk of bias of outcomes across all studies was similar and predominately low.

Palivizumab reduces hospitalisation due to RSV infection at two years' follow-up (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.30 to 0.64; 5 studies, 3343 participants; high certainty evidence). Based on 98 hospitalisations per 1000 participants in the placebo group, this corresponds to 43 (29 to 62) per 1000 participants in the palivizumab group. Palivizumab probably results in little to no difference in mortality at two years' follow-up (RR 0.69, 95% CI 0.42 to 1.15; 5 studies, 3343 participants; moderate certainty evidence). Based on 23 deaths per 1000 participants in the placebo group, this corresponds to 16 (10 to 27) per 1000 participants in the palivizumab group. Palivizumab probably results in little to no difference in adverse events at 150 days' follow-up (RR 1.09, 95% CI 0.85 to 1.39; 3 studies, 2831 participants; moderate certainty evidence). Based on 84 cases per 1000 participants in the placebo group, this corresponds to 91 (71 to 117) per 1000 participants in the palivizumab group. Palivizumab probably results in a slight reduction in hospitalisation due to respiratory-related illness at two years' follow-up (RR 0.78, 95% CI 0.62 to 0.97; 5 studies, 3343 participants; moderate certainty evidence). Palivizumab may result in a large reduction in RSV infection at two years' follow-up (RR 0.33, 95% CI 0.20 to 0.55; 3 studies, 554 participants; low certainty evidence). Based on 195 cases of RSV infection per 1000 participants in the placebo group, this corresponds to 64 (39 to 107) per 1000 participants in the palivizumab group. Palivizumab also reduces the number of wheezing days at one year's follow-up (RR 0.39, 95% CI 0.35 to 0.44; 1 study, 429 participants; high certainty evidence).

Authors' conclusions

The available evidence suggests that prophylaxis with palivizumab reduces hospitalisation due to RSV infection and results in little to no difference in mortality or adverse events. Moreover, palivizumab results in a slight reduction in hospitalisation due to respiratory-related illness and may result in a large reduction in RSV infections. Palivizumab also reduces the number of wheezing days. These results may be applicable to children with a high risk of RSV infection due to comorbidities.

Further research is needed to establish the effect of palivizumab on children with other comorbidities known as risk factors for severe RSV disease (e.g. immune deficiencies) and other social determinants of the disease, including children living in low- and middle-income countries, tropical regions, children lacking breastfeeding, living in poverty, or members of families in overcrowded situations.

PLAIN LANGUAGE SUMMARY

Palivizumab for respiratory syncytial virus infection prevention in children

Review question

What are the effects (benefits and harms) of palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children?

Background

RSV is the main cause of acute respiratory infections in children, mainly during the first year of life, accounting for 33.1 million infections a year with an estimated 90.6% of these episodes occurring in low- and middle-income countries. These infections may present with a runny nose, fever, cough, shortness of breath, wheezing, or difficulty feeding. They may result in hospitalisation, admission to an intensive care unit, and even death, in particular amongst infants aged less than two months, with an estimated hospitalisation rate of 1970 per 100,000 population and 59,600 deaths annually worldwide in children younger than five years old. They may also lead to long-term complications such as recurrent wheezing and chronic lung problems.

Palivizumab, sold under the brand name Synagis, is a drug administered with an intramuscular injection every month up to five doses to prevent serious infections in children at high risk for severe disease.

Search date

The evidence is current to 14 October 2021.

Study characteristics

We included five studies with 3343 participants. All studies included a small number of participants, including children with a high risk of adverse outcomes if infected with RSV due to underlying health issues, such as premature birth or heart or pulmonary problems.

Study funding sources

Most studies did not specify their funding sources. One study was funded by Abbott Laboratories and by the Netherlands Organisation for Health Research and Development.

Key results

Palivizumab reduces hospitalisation due to RSV infection by 56%; based on 98 cases per 1000 participants in the placebo group, this corresponds to 43 per 1000 participants in the palivizumab group. Palivizumab probably results in little to no difference in mortality, and little to no difference in adverse events; based on 23 deaths per 1000 participants and 84 adverse events per 1000 participants in the placebo group, this corresponds to 16 deaths per 1000 participants and 81 adverse events per 1000 participants in the palivizumab group. Palivizumab probably results in a slight reduction in hospitalisation due to respiratory illness by 22% but may result in little to no difference in length of hospital stay. It may reduce RSV infection rate by 67% at two years' follow-up. Palivizumab also reduces the number of wheezing days by 61% but may result in little to no difference in days using oxygen, length of stay in the intensive care unit, or mechanical ventilation days.

Certainty of the evidence

The overall certainty of the evidence was moderate to high.

Summary of findings 1. Palivizumab compared to placebo, no intervention or standard care for preventing respiratory syncytial virus (RSV) infection in children

Palivizumab compared to placebo, no intervention or standard care for preventing respiratory syncytial virus (RSV) infection in children

Patient or population: children (0 to 24 months)

Setting: inpatients and outpatients

Intervention: palivizumab

Comparison: placebo, no intervention or standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with palivizumab				
Hospitalisation due to RSV infection *Follow-up: 2 years*	98 per 1000	**43 per 1000** (29 to 62)	**RR 0.44** (0.30 to 0.64)	3343 (5 RCTs)	⨁⨁⨁⨁ HIGH	
Mortality *Follow-up: 2 years*	23 per 1000	**16 per 1000** (10 to 27)	**RR 0.69** (0.42 to 1.15)	3343 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	
Adverse events *Follow-up: 150 days*	84 per 1000	**91 per 1000** (71 to 117)	**RR 1.09** (0.85 to 1.39)	2831 (3 RCTs)	⨁⨁⨁◯ MODERATE[b]	
Hospitalisation due to respiratory-related illness *Follow-up: 2 years*	351 per 1000	**274 per 1000** (218 to 340)	**RR 0.78** (0.62 to 0.97)	3343 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	
RSV infection *Assessed with: incidence of laboratory-confirmed RSV-bronchiolitis* *Follow-up: 2 years*	195 per 1000	**64 per 1000** (39 to 107)	**RR 0.33** (0.20 to 0.55)	554 (3 RCTs)	⨁⨁◯◯ LOW[c]	
Number of wheezing days	45 per 1000	**18 per 1000**	**RR 0.39**	429	⨁⨁⨁⨁	

Assessed with: rates of wheezing per day *Follow-up: 12 months*		(16 to 19)	(0.35 to 0.44)	(1 RCT)	HIGH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to imprecision. The 95% confidence interval includes appreciable benefit and little to no effect.
[b]Downgraded 1 level due to imprecision. The 95% confidence interval includes appreciable benefit and harm.
[c]Downgraded 2 levels due to few number of events and participants in both groups.

BACKGROUND

Description of the condition

Respiratory viruses are the leading cause of lower respiratory tract infection (LRTI) and hospitalisation in infants and young children (Nair 2010; Nair 2011). Globally, respiratory syncytial virus (RSV) is the main infectious agent every year in this population (Nair 2010; Shi 2017). Over the past 15 years, there has been a significant reduction in child pneumonia mortality and morbidity due to the successful implementation of new vaccine schedules for *Haemophilus influenzae* and *Streptococcus pneumoniae* (Shi 2017). In this context of scale-up in vaccines, the burden of RSV disease continues to increase (Shi 2017).

RSV, now reclassified as a member of the *Pneumoviridae* family and *Orthopneumovirus* genus (Amarasinghe 2019), was first identified in 1956 (Chanock 1957). Its viral genome, a single-stranded and negative sensed ribonucleic acid (RNA), codes for 11 proteins (nine structural proteins and two non-structural proteins) (Gálvez 2017; Hacking 2002). Transmission of the virus occurs mainly due to contact with contaminated secretions, including surfaces (where RSV can survive for several hours), hands, and direct contact with respiratory secretions. Inoculation develops in the upper respiratory tract, with subsequent infection of the respiratory epithelium, triggering the main infectious mechanisms to survive. Once infected, the incubation period may last four to five days (Lessler 2009).

The seasonality of RSV infection varies according to the location, with considerable fluctuations each year (Mullins 2003). Understanding RSV seasonality has become essential in order to determine the month in which to start immunoprophylaxis for vulnerable populations. In temperate climates, there is a clear affinity for colder seasons (Northern Hemisphere: November to April; Southern Hemisphere: April to September). However, in regions with tropical and subtropical climates, RSV may be present throughout the whole year, probably correlating with rainy seasons (Brady 2014; Hall 2009).

In the USA, RSV is one of the main causes of hospitalisation, in particular amongst infants aged less than two months, with an estimated hospitalisation rate of 1970 per 100,000 population (95% confidence interval (CI), 1787 to 2177) (Arriola 2019). Furthermore, RSV infected children in the USA, present a higher average of all-cause cumulative hospitalisations rates, for at least five years after the initial infection (Simões 2020). However, the burden of the disease, the number of infected per total population, and the short- and long-term complications are considerably lower in high-income countries (HIC) (Arriola 2019; Shi 2017). In the Western Pacific Region, the incidence of RSV hospitalisation ranged between 4.9 and 30.9 per 1000 child-years, varying according to age group (Pangesti 2019).

Globally, RSV accounts for 33.1 million (uncertainty range (UR) 21.6 to 50.3) LRTI a year in children younger than five years old, mainly during the first year of life (Shi 2017), with an estimate of 90.6% (30.0 million) of these episodes occurring in low- and middle-income countries (LMIC) (Shi 2017). More than three million (UR 2.7 to 3.8) hospital admissions worldwide in young children are due to RSV LRTI, with the highest rate in children younger than six months old, in particular in neonates with 15.9 (95% CI 8.8 to 28.9) admissions per year in LMIC (Nair 2010; Shi 2017). Severe RSV LRTI (hypoxaemia) accounts for 1.0 million (UR 0.6 to 1.6) hospital admissions, and very severe LRTI (hospitalised LRTI with danger signs like cyanosis, difficulty in breastfeeding or drinking, vomiting, convulsions, lethargy, unconsciousness, head nodding or ICU admission/mechanical ventilation) for 0.6 million (UR 0.4 to 1) every year in LMIC, mostly in children younger than six months old (Shi 2017).

Regarding mortality, RSV is one of the leading causes of death in the paediatric population (Scheltema 2017; WHO 2018), with a worldwide annual estimate of 59,600 fatalities (UR 48,000 to 74,500) in children younger than five years old (Nair 2013). Most deaths occur in previously healthy children, in particular, in LMIC (Geoghegan 2017; Hall 2009; Hall 2013). In HIC, mortality cases are usually in older children who have a higher prevalence of comorbidities (7.0 years interquartile range (IQR) 3.6 to 16.8 and 70%, respectively) than in upper middle-income countries (4 years IQR 2.0 to 10.0 and 47%) and LMIC (5 months IQR 2.3 to 11.0 and 28%) (Scheltema 2017). As expected, the case fatality rate is higher in children with comorbidities, in particular, those with chronic lung diseases, congenital heart disease, premature birth, Down's syndrome, and a diagnosis of sepsis or pneumothorax during hospitalisation (Geoghegan 2017; Lee 2016; Thorburn 2009; Welliver 2010). To add to this burden of disease of RSV LRTI, there is a considerable proportion of children who die at home without being hospitalised, in particular in LMIC, a reflection of limited access to hospital care (Caballero 2019; Shi 2017).

RSV infection has a significant economic burden on the health system, for example, in the USA, the total annual direct medical costs for all RSV infections in children younger than five years old is USD 652 million per year (USD 394 million from hospitalisations and USD 258 million from other medical encounters) (Paramore 2004). In LMIC, the cost of each RSV episode is less expensive, but due to the larger proportion of RSV infections, the economic burden may be more significant (Zhang 2016).

At an individual level, almost every child has been infected with the virus by the age of two years (Feldman 2015; Holberg 1991). Signs and symptoms range from an upper respiratory tract infection (nasal congestion, fever, cough, rhinorrhoea) or a LRTI (bronchiolitis or pneumonia) with difficulty breathing, wheezing, difficulty in feeding, or apnoea (Arms 2008; Domachowske 1999). Severity depends on the damage inflicted by the virus and the efficiency of the triggered immune response. Most children will only require ambulatory management, and only a few will need admission to a general ward (1% to 3%) Boyce 2000, or an ICU (less than 1%) (Bont 2016; Hervás 2012; Shay 2001). Children at higher risk for RSV life-threatening disease include those with congenital heart disease, preterm birth, chronic lung disease, pulmonary hypertension and immunodeficiency (Damore 2008; Mansbach 2012; Purcell 2004). RSV infections in children, in particular those episodes requiring hospitalisation, are associated not only with acute complications but also with long-term complications such as recurrent wheezing, impaired lung function and paediatric asthma (Esteban 2020; Fauroux 2017; Sigurs 2005; Singh 2007; Thomsen 2009).

Description of the intervention

Palivizumab is a humanised monoclonal antibody (mAb) against RSV fusion (F) glycoprotein, inhibiting RSV replication (Johnson 1997). It was first licenced under the name of Synagis in the

USA. Trials were first conducted in 1996, published in 1998 with subsequent Food and Drug Administration (FDA) approval, proving safety and efficacy in highly vulnerable conditions (premature children born before 35 weeks and children with bronchopulmonary dysplasia) (IMpact-RSV Study Group 1998). Following approval by the European Medicines Agency in 1999, the use of the drug became worldwide (SYNAGIS ® (palivizumab)).

The drug is administered intramuscularly on a monthly basis during the infant's first RSV season (up to five doses at a dose of 15 mg/kg) to prevent serious RSV LRTI. In some cases, children with bronchopulmonary dysplasia or congenital heart disease receive a second season of the drug. Monoclonal antibodies promote a response that depends entirely from the given half-life of the antibody in the host, without activating the immune system or inducing immunological memory, hence the requirement of monthly injection of palivizumab (Baxter 2007; Soto 2020).

Candidates for immunoprophylaxis with palivizumab have changed over the past 22 years, depending on countries' public health policy. Since 2014, the American Academy of Pediatrics Guidelines indications have become more restrictive (Brady 2014), with results still inconclusive regarding guidelines impact, however, with a worrying trend towards an increase in the number of RSV-related hospitalisations (Capizzi 2017; Goldstein 2018; Krilov 2020; Zembles 2019). Nevertheless, at least 30% of individuals who receive palivizumab do not fit these recommendations, probably because palivizumab is the only available pharmacological prevention strategy against RSV (Trist 2018).

Since its first use, palivizumab has proved to be effective in several clinical trials in different settings (Anderson 2017; IMpact-RSV Study Group 1998; Moore 2019). In a Cochrane Review from 2013, a significant effect was seen for palivizumab in preventing hospitalisations when compared to placebo (risk ratio 0.49, 95% CI 0.37 to 0.64) (Andabaka 2013). However, the cost of the medication remains high at USD 1416 per 100 mg. This is an important obstacle for its use, particularly in LMIC. This has led to a cost-effectiveness analysis in different countries, settings, and conditions (Andabaka 2013). Although it has been proven cost-effective in some countries (Mac 2019; Schmidt 2017), studies in Israel and Germany tend to disagree affirming that a substantial decrease in the cost (36.8% to 83.3%) is needed in order to be a cost-effective strategy amongst vulnerable populations (Blanken 2013; Ginsberg 2018). As a consequence of its high economic burden, different studies have assessed whether a shorter course of palivizumab would provide the same efficacy and same RSV antibody levels than the regular five doses with inconclusive results (Claydon 2017; Claydon 2019; La Via 2013; Moore 2019; Robbie 2012).

Other pharmacologic strategies have been assessed since RSV was first identified in 1956, and several are now under investigation and development (Mejias 2015; Simões 2018; Tripp 2017). Palivizumab was also tested as an intravenous infusion during an acute RSV episode, but showed no benefit (Alansari 2019), nor did RSV immunoglobulin (Sanders 2019). In 2008, motavizumab, a mAb also used against RSV F glycoprotein, but with a 70-fold increase in affinity compared to palivizumab was tested for preventing RSV LRTI (Fernández 2010). Although it proved to be more efficient than palivizumab in preventing RSV hospitalisations, it was not approved by the FDA due to dermatological side effects (Carbonell-Estrany 2010). Other mAbs under investigation include human IgA antibody formats of palivizumab and motavizumab (Jacobino 2018), anti RSV G glycoprotein or N-protein (Tripp 2017) and mAbs with a longer half-life (Griffin 2020; Zhu 2017).

How the intervention might work

Palivizumab is a humanised monoclonal immunoglobulin G1, directed against an epitope of RSV surface glycoprotein F (Johnson 1997). When binding to it, palivizumab prevents the fusion of the viral particle and host cell membrane (avoiding the entry of the viral genome used for replication and transcription) and might also suppress the syncytia formation in respiratory epithelial cells (Soto 2020; Young 2002). In addition, palivizumab diminishes viral activity and cell-to-cell transmission, reducing RSV virulence and its risk of developing RSV LRTI (Collins 2011).

Why it is important to do this review

In 2013, a Cochrane Review assessed the role of palivizumab in preventing RSV LRTI (Andabaka 2013). Since then, many trials have continued evaluating its effectiveness and defining its usefulness in different subpopulations. A non-Cochrane systematic review on the topic was published in 2014 with methodological limitations (Wegzyn 2014), such as the lack of risk of bias assessment. Given the high cost of the drug, it is essential to know if palivizumab continues to be effective in preventing severe RSV disease in high-risk children. Meanwhile, the proportion of RSV infections continues to rise, especially in LMIC; despite the probable changing landscape regarding RSV interventions, palivizumab continues to be the only approved RSV-related drug. Our main goal is to provide a high-quality review of the evidence on the effects of palivizumab in preventing severe RSV infection in children.

OBJECTIVES

To assess the effects of palivizumab for preventing severe respiratory syncytial virus infection in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including cluster-RCTs. We did not include cross-over RCTs as they are not relevant to the review question. We included studies reported as full text, those published as abstract only, and unpublished data where it was possible to establish eligibility for inclusion when data were limited. There were no language or publication restrictions.

Types of participants

We included children (0 to 24 months of age) of both genders, regardless of RSV infection history. We included children with immunodeficiency disorders. We excluded children with cystic fibrosis, as a related Cochrane Review has already been published on that topic (Robinson 2016).

Types of interventions

We included trials comparing palivizumab given intramuscularly or intravenously at a dose of 15 mg/kg once a month (maximum five doses) with placebo, no intervention or standard care alone (oxygen supplementation, bronchodilators, corticosteroids, intravenous fluids, etc). We included co-interventions (e.g.

corticosteroids) provided they were not part of the randomised treatment and were consistent across groups.

Types of outcome measures

The outcomes listed here were not eligibility criteria for this review but were outcomes of interest within the included studies.

Primary outcomes

1. Hospitalisation due to RSV infection: defined as the number of children hospitalised with laboratory-confirmed infection.
2. Mortality: death due to all causes. We also reported the cause of deaths for each group (including deaths related to RSV infection).
3. Adverse events: defined as any unexpected or harmful occurrence in the participant, such as rash, pain in the injection site, fever, nausea, vomiting, diarrhoea, etc., reported in absolute numbers or proportions. We intended to report non-serious and serious adverse events (including death, disability, life-threatening events or those requiring hospitalisations) separately. Had there been multiple events reported within one participant, we would have reported this separately.

Secondary outcomes

1. Hospitalisation due to respiratory-related illness: defined as the number of children needing admission to hospital for treatment of respiratory symptoms without alternative aetiology and with negative RSV antigen test or no test done.
2. Length of hospital stay: number of days in which a child has been hospitalised due to RSV infection or respiratory-related illness.
3. RSV infection: incidence of laboratory-confirmed RSV-bronchiolitis.
4. Number of wheezing days: wheeze or bronchodilator medication use reported by parents.
5. Days of supplemental oxygen.
6. Intensive care unit length of stay.
7. Mechanical ventilation days.

For continuous outcomes only available in a subset of participants (length of hospital stay, number of wheezing days, days of supplemental oxygen, ICU length of stay, mechanical ventilation days) we presented the data as days per 100 randomised children following the guidance in Section 6.9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

Timing of outcome measurement

We considered outcomes measured up to and including 12 months after randomisation as short term and more than 12 months as long term. When multiple results were reported for each outcome, we included the longest follow-up in each category.

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the date of search with no restrictions on the language of publication or publication status:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (2021, Issue 10) searched 14 October 2021;
2. MEDLINE (Ovid) from 1946 to 14 October 2021;
3. Embase (Elsevier.com) from 1947 to 15 October 2020;
4. Latin American and Caribbean Health Science Information database (LILACS) (BIREME) from 1982 to 14 October 2021;
5. CINAHL (Cumulative Index to Nursing and Allied Health Literature) from 1981 to 14 October 2021; and
6. Scopus from 1970 to 14 October 2021.

For detailed search strategies, see Appendix 1.

Searching other resources

We attempted to identify other potentially eligible studies or ancillary publications by searching the reference list of included studies, systematic reviews, meta-analyses, and health technology assessment reports. We contacted experts in the field to identify additional unpublished materials. We searched the websites of relevant manufacturers for information on trials. We sought errata or retractions of the included studies. We contacted authors of the included studies to identify other unpublished studies. We searched for registered and ongoing trials in the following trial registers:

1. ClinicalTrials.gov (www.ClinicalTrials.gov) searched 14 October 2021; and
2. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch/) searched 14 October 2021.

For detailed search strategies, see Appendix 1.

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs, and if appropriate, Cochrane Crowd – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, visit the Screen4Me webpage on the Cochrane Information Specialist's portal: https://community.cochrane.org/organizational-info/resources/resources- groups/information-specialists-portal. More detailed information regarding evaluations of the Screen4Me components can also be found in the following publications: Marshall 2018; Noel-Storr 2020; Noel-Storr 2021;Thomas 2020.

Two review authors (LG, LS) independently screened the titles and abstracts of studies we identified as a result of the search for potential inclusion in the review.

We retrieved the full-text study reports/publications deemed potentially eligible, and two review authors (LG, LS) independently screened the full texts and identified studies for inclusion and identified and recorded reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (JVAF) when required. We identified and excluded duplicates and collated multiple reports

of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009). We used Covidence software for study selection (Covidence). We did not impose any language restrictions.

Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. One review author (LG or LS) extracted study characteristics from the included studies. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, RSV infection history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (LG, LS) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. Any disagreements were resolved by consensus or by involving a third review author (JVAF). One review author (LG) transferred data into Review Manager 5 software (Review Manager 2020). A second review author (JVAF) double-checked that data had been entered correctly by comparing the data presented in the systematic review with the study reports. The second review author (JVAF) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (LG, LS) independently assessed risk of bias of the results of the main outcomes (those included in the Summary of findings 1, see below) in each study using a recently developed revision of the Cochrane risk of bias tool (RoB 2: a revised tool to assess the risk of bias in randomised trials) (Higgins 2019a; Sterne 2019). Any disagreements were resolved by discussion or by involving another review author (JVAF). We assessed risk of bias according to the following domains.

1. The randomisation process.
2. Deviations from intended interventions.
3. Missing outcome data.
4. Measurement of the outcome.
5. Selection of the reported results.

Answers to signalling questions and supporting information collectively led to a domain-level judgement in the form of 'low risk', 'some concerns', or 'high risk' of bias. These domain-level judgements informed an overall risk of bias judgement for the outcome. We considered the algorithm proposed judgements and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We also provided reasons for judgments that did not follow the algorithm. We summarised the risk of bias judgements across different studies for each of the domains listed. When judging the bias due to deviations from intended interventions, we focused the analyses on the effect of assignment to intervention (Higgins 2019a). We aimed to source published protocols for the assessment of selective reporting. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table.

We used the 22 August 2019 version of the RoB 2 Excel tool to manage the data supporting the answers to the signalling questions and risk of bias judgements (available at https://www.riskofbias.info/). All these data are publicly available as supplementary material in the Open Science Framework platform (osf.io/).

For cluster-RCTs, we would have used the RoB 2 tool and added an additional domain specific to cluster RCTs from the archived version of the tool (Domain 1b - 'Bias arising from the timing of identification and recruitment of participants'; see https://www.riskofbias.info/) with its corresponding signalling questions, following the guidance in Section 23.1.2 and Table 23.1.a of the Cochrane Handbook (Higgins 2019c).

We made summary assessments of the risk of bias for each short- and long-term result for each outcome (across domains) within and across studies (Higgins 2019a).

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We entered the outcome data for each study into data tables in Review Manager 5 to calculate the treatment effects (Review Manager 2020).

We analysed dichotomous data as risk ratios (RRs) and continuous data as mean difference (MD). We reported corresponding 95% confidence intervals (CIs). We entered data presented as a scale with a consistent direction of effect.

We undertook meta-analyses only where this was meaningful, that is if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

Unit of analysis issues

Where multiple trial arms were reported in a single trial, we included only the treatment arms relevant to the review topic. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same study, we would have followed the guidance in Section 6.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting (Higgins 2019b). Our preferred approach would have been to combine groups to create a single pair-wise comparison. For cluster-RCTs, we would have considered the cluster as the unit of analysis, not the individual participant, in order to avoid unit of analysis errors, as stated in Section 23.1.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b)

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only).

If numerical outcome data such as standard deviations or correlation coefficients were missing, and they could not be obtained from the authors, we calculated them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b).

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity amongst the trials in each analysis. If we identified substantial heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis.

We used the rough guide to interpretation as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b), as follows:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity; and
4. 75% to 100%: considerable heterogeneity.

We avoided the use of absolute cut-off values but interpreted I^2 in relation to the size and direction of effects and strength of evidence for heterogeneity. We performed a random-effects meta-analysis, which accounts for between-study heterogeneity.

Assessment of reporting biases

If there were more than 10 trials, we would create and examin a funnel plot to explore possible small-study and publication biases. If searches identified trial protocols, clinical trial registrations or abstracts indicating the existence of unpublished studies, we attempted to determine the status of any unpublished studies through contact with the investigators.

We considered outcome reporting bias in our risk of bias assessments.

Data synthesis

We pooled data from studies judged to be clinically homogeneous using Review Manager 5 software (Review Manager 2020). If more than one study provided useable data in any single comparison, we performed a meta-analysis. We used a random-effects model, as this is usually a more conservative approach. We included all studies in the primary analysis and planned to explore the effect of bias in a sensitivity analysis (see Sensitivity analysis).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. High-risk children (e.g. children with heart disease, respiratory diseases, premature children, children with low birth weight) versus average-risk children.
2. Tropical regions versus non-tropical regions.
3. High-income countries versus low- and middle-income countries

We were only able to carry out the subgroup analysis for high-income countries versus low- and middle-income countries, and only for the outcome hospitalisation due to respiratory-related illness.

We used the Chi^2 test to test for subgroup interactions in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

We had planned to carry out the following sensitivity analyses:

1. Repeated the analysis excluding unpublished studies (if there were any).
2. Repeated the analysis excluding studies at an overall high risk of bias.
3. Repeated the analysis excluding small studies (if there were any).

However, no studies fitted the criteria.

Summary of findings and assessment of the certainty of the evidence

We created Summary of findings 1 using the following outcomes:

1. hospitalisation due to RSV infection (long term);
2. mortality (long term);
3. adverse events (non-serious/serious: long term);
4. hospitalisation due to respiratory-related illness (long term);
5. RSV infection (long-term); and
6. number of wheezing days (three to six years).

Two review authors (LG, LS) used the five GRADE considerations (overall RoB 2 judgement, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b) emplying GRADEproGDT software (GRADEpro GDT). Any disagreements were resolved by discussion or by involving another review author (JVAF). We assessed evidence certainty according to the GRADE criteria. We considered RCTs as high certainty evidence if the five factors above related to risk if bias (see Assessment of risk of bias in included studies) were not present to any serious degree, but downgraded the certainty to moderate, low or very low as needed. We downgraded the certainty of the evidence once if a GRADE consideration was serious, and twice if very serious. We justified all decisions to down- or upgrade the certainty of the evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

For study details, see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

For a detailed description of our screening process, see the study flow diagram (Figure 1).

Figure 1. Flow diagram

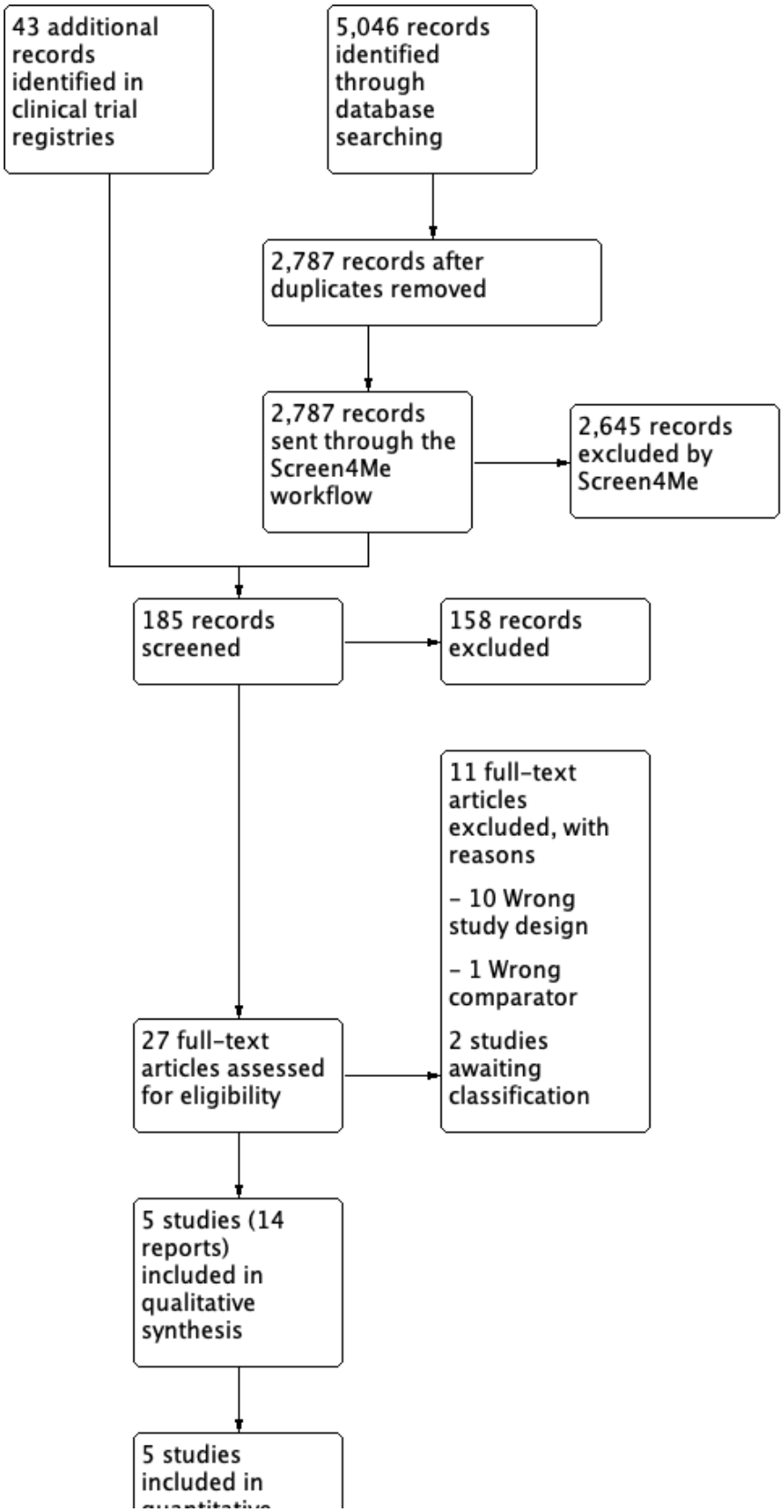
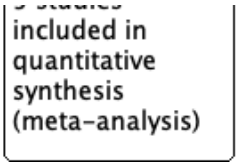
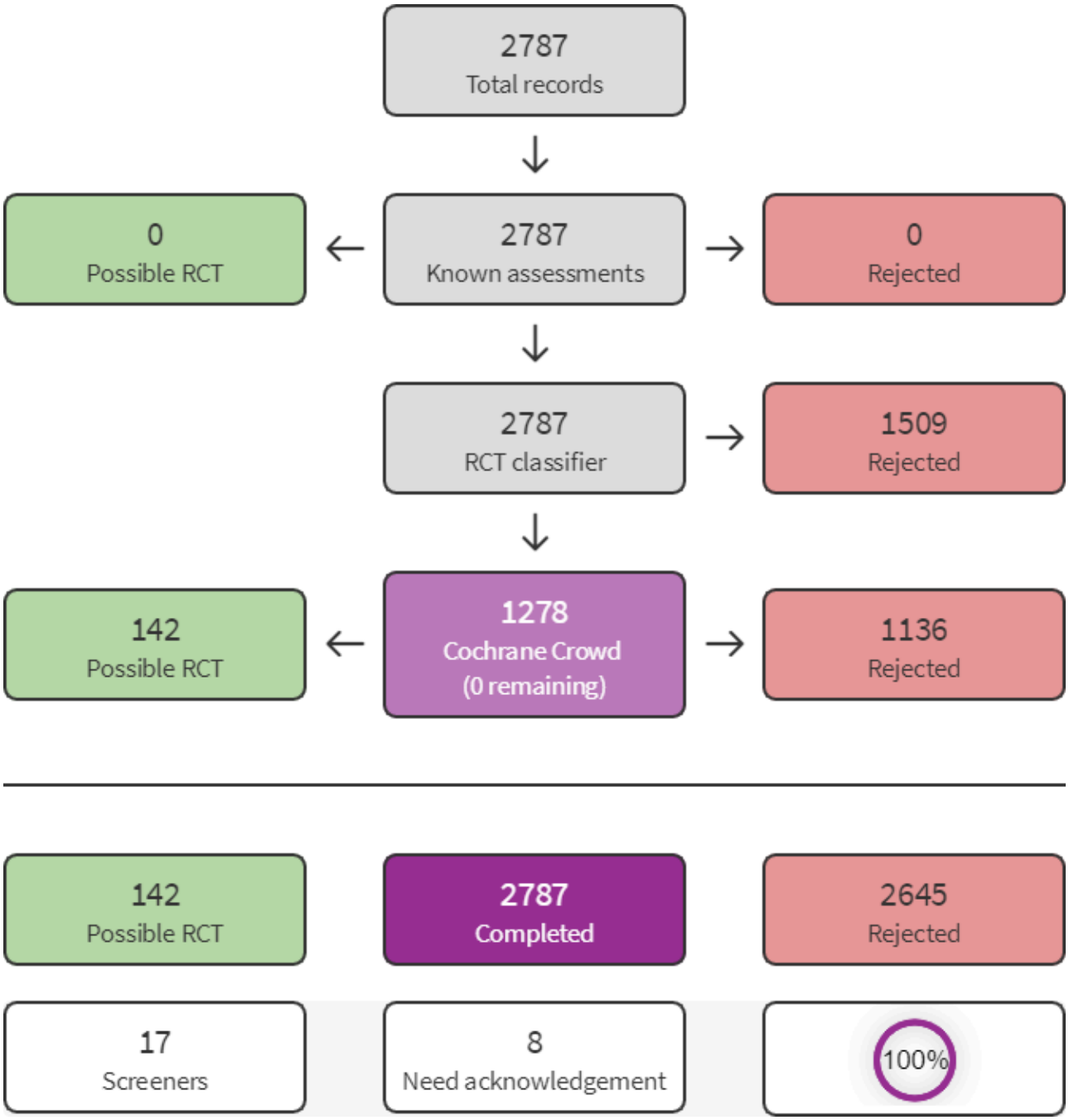


Figure 1. (Continued)



The searches of the databases identified a total of 5046 search results of which 2787 records remained after deduplication. In assessing the studies, we used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials. The results of the Screen4Me assessment process are provided in Figure 2. We then assessed the remaining 142 records left after Screen4Me. Our searches of the trial registers identified a further 43 studies. Our screening of the reference lists of the included publications did not reveal any additional RCTs. We therefore had a total of 185 records of which 158 records were excluded based on title and abstract. We obtained the full texts of the remaining 27 records. We excluded 11 studies (see Characteristics of excluded studies). We added two records to Characteristics of studies awaiting classification. We did not identify any ongoing studies.

Figure 2. Screen4Me summary diagram



We finally included five studies reported in 14 references.

Included studies

We included five studies with a total 3343 participants (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014).

Designs

All studies were parallel RCTs (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014).

Sample sizes

The median sample size was 429 participants (interquartile range 83 to 1287). The largest sample size was 1502 participants (IMpact-RSV Study Group 1998) and the smallest was 42 participants (Subramanian 1998).

Settings

All studies were conducted in an outpatient setting (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014). One study also included neonatal ICU hospitalised infants (Tavsu 2014).

Four of the included studies were multicentre studies (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998). Two of these studies were also multinational studies (Feltes 2003; IMpact-RSV Study Group 1998), conducted in the United States, Canada, Sweden, Germany, Poland, France and the United Kingdom. The other two multicentre studies were conducted in the United States, Subramanian 1998, and the Netherlands, Blanken 2013. One study was a single-centre study conducted in Turkey (Tavsu 2014).

All studies were reported in the English language.

Participants

Three studies included infants 24 months of age or younger at the start of the RSV season with a gestational age of 35 weeks or less (Blanken 2013; IMpact-RSV Study Group 1998; Subramanian 1998). One study included infants with a gestational age of 32 weeks or younger who were hospitalised in the neonatal ICU, infants 12 months of age or less at the beginning of the RSV season with a gestational age of 28 weeks, and infants born at 29 to 32 weeks of gestational age who were younger than six months old at the beginning of RSV season (Tavsu 2014). Two studies included children who had bronchopulmonary dysplasia (BPD) and were 24 months of age or younger (IMpact-RSV Study Group 1998; Subramanian 1998). Finally, one study included children 24 months old or younger at the time of randomisation with documented haemodynamically significant congenital heart disease (CHD) determined by the investigator and had unoperated or partially corrected CHD (Feltes 2003).

Interventions

In all of the included trials, palivizumab was delivered intramuscularly, except for one study in which it was delivered intravenously (Subramanian 1998). All studies delivered 15 mg/kg doses. One study was a dose-escalation study, testing three different doses (Subramanian 1998); only data for the recommended approved dose of 15 mg/kg were included in our analyses. Four studies compared palivizumab against placebo (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998), and one study compared palivizumab versus no intervention (Tavsu 2014).

Outcomes

All studies reported the effect of the intervention on hospitalisation due to RSV infection, all-cause mortality, and hospitalisations due to respiratory-related illness. Three studies reported adverse events (Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998). Three studies reported RSV infection (Blanken 2013; Subramanian 1998; Tavsu 2014). Two studies reported length of hospital stay, days of supplemental oxygen, intensive care unit length of stay, and mechanical ventilation days (Feltes 2003; IMpact-RSV Study Group 1998). One study reported the number of wheezing days (Blanken 2013).

Funding sources

Most studies (four of five studies, 80%) did not specify their funding sources. Blanken 2013 was funded by Abbott Laboratories (Abbott International PLC (UK)) and the Netherlands Organisation for Health Research and Development, with no restrictions for publication of the research data.

Excluded studies

We excluded 11 reports after full-text assessment. One report compared palivizumab against motavizumab (EUCTR2007-002070-61-PL). Two reports were informative summaries with no authors declared and no original research data reported (Anonymous 1999; Anonymous 2004). One report was a narrative review (Driver 1999). Another report was an evidence synopsis (Ignacio 2013). The remaining six reports were observational studies (Johnson 1999; Koganesawa 2019; Naver 2002; Pin 2002; Rajakumar 2009; Tulloh 2011).

Risk of bias in included studies

The risk of bias assessments for each outcome, including all domain judgements and support for judgement, are provided in the risk of bias tables within the Characteristics of included studies section and at the side of all forest plots. To access the further detailed risk of bias assessment data, visit https://osf.io/26dns/ (DOI 10.17605/OSF.IO/26DNS).

Risk of bias was similar across most outcomes, judged as 'low'. The only exception was outcomes reported by one study (Tavsu 2014) which were judged as 'some concerns'. This trial did not adequately describe allocation concealment and, unlike the other trials, it compared palivizumab to 'no intervention', which raised concerns due to deviations from intended interventions, as this was not adequately described. This study reported hospitalisations (due to respiratory illness and RSV infection), mortality and RSV infection. However, this did not affect our GRADE judgement for these results considering the trial's relative contribution to the overall estimate.

Effects of interventions

See: **Summary of findings 1** Palivizumab compared to placebo, no intervention or standard care for preventing respiratory syncytial virus (RSV) infection in children

1. Palivizumab versus placebo or no intervention

Five studies with a total of 3343 participants were included in this comparison (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014). See Summary of findings 1.

Primary outcomes

1.1. Hospitalisation due to RSV infection

Five studies with 3343 participants reported this outcome (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014). Palivizumab reduces hospitalisation due to RSV infection compared to placebo or no intervention at two years' follow-up (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.30 to 0.64; I^2 = 23%; Analysis 1.1). We assessed the evidence for this outcome as of high certainty.

1.2 Mortality

Five studies with 3343 participants reported this outcome (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014). Palivizumab probably results in little to no difference in mortality compared to placebo or no intervention at two years' follow-up (RR 0.69, 95% CI 0.42 to 1.15; I^2 = 0%; Analysis 1.2). We assessed the evidence for this outcome as of moderate certainty due to concerns about imprecision.

1.3 Adverse events

Three studies with 2831 participants reported this outcome (Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998). Palivizumab probably results in little to no difference in adverse events compared to placebo or no intervention at 150 days' follow-up (RR 1.09, 95% CI 0.85 to 1.39; I^2 = 0%; Analysis 1.3). We assessed the evidence for this outcome as of moderate certainty due to concerns about imprecision.

Secondary outcomes

1.4 Hospitalisation due to respiratory-related illness

Five studies with 3343 participants reported this outcome (Blanken 2013; Feltes 2003; IMpact-RSV Study Group 1998; Subramanian 1998; Tavsu 2014). Palivizumab probably results in a slight reduction in hospitalisation due to respiratory-related illness compared to placebo or no intervention at two years' follow-up (RR 0.78, 95% CI 0.62 to 0.97; I^2 = 45%; Analysis 1.4). We assessed the evidence for this outcome as of moderate certainty due to concerns about imprecision.

1.5 Subgroup analysis: hospitalisation due to respiratory-related illness

We found that palivizumab results in a higher reduction in hospitalisation due to respiratory-related illness in lower-middle-ime countries (LMIC) (RR 0.47, 95% CI 0.18 to 1.22) compared to HIC (RR 0.80, 95% CI 0.65 to 0.99) (test for subgroup differences: P = 0.28, I^2 = 14.0%; Analysis 1.5).

1.6 Length of hospital stay

Two studies with 2789 participants reported this outcome (Feltes 2003; IMpact-RSV Study Group 1998). Palivizumab may result in little to no difference in length of hospital stay compared to placebo or no intervention at 150 days' follow-up (mean difference (MD) -42.24, 95% CI -84.77 to 0.29; I^2 = 64%; Analysis 1.6).

1.7 RSV infection

Three studies with 554 participants reported this outcome (Blanken 2013; Subramanian 1998; Tavsu 2014). Palivizumab may result in a large reduction in RSV infection compared to placebo or no intervention at two years' follow-up (RR 0.33, 95% CI 0.20 to 0.55; I^2 = 0%; Analysis 1.7). We assessed the evidence for this outcome as of low certainty due to serious concerns about imprecision.

1.8 Number of wheezing days

One study with 429 participants reported this outcome (Blanken 2013). Palivizumab reduces the daily rate of wheezing compared to placebo or no intervention at one year's follow-up (RR 0.39, 95% CI 0.35 to 0.44; Analysis 1.8) We assessed the evidence for this outcome as of high certainty.

1.9 Days of supplemental oxygen

Two studies with 2789 participants reported this outcome (Feltes 2003; IMpact-RSV Study Group 1998). Palivizumab may result in little to no difference in days of supplemental oxygen compared to placebo or no intervention at 150 days' follow-up (MD -36.85, 95% CI -85.19 to 11.49; I^2 = 59%; Analysis 1.9).

1.10 Intensive care unit length of stay

Two studies with 2789 participants reported this outcome (Feltes 2003; IMpact-RSV Study Group 1998). Palivizumab may result in little to no difference in intensive care unit length of stay compared to placebo or no intervention at 150 days' follow-up (MD -13.51, 95% CI -61.11 to 34.08; I^2 = 50%; Analysis 1.10).

1.11 Mechanical ventilation days

Two studies with 2789 participants reported this outcome (Feltes 2003; IMpact-RSV Study Group 1998). Palivizumab may result in little to no difference in mechanical ventilation days compared to placebo or no intervention at 150 days' follow-up (MD 5.78, 95% CI -10.37 to 21.92; I^2 = 0%; Analysis 1.11).

DISCUSSION

Summary of main results

We included five studies with a total of 3343 participants assessing the effect of palivizumab compared to placebo or no intervention for preventing severe RSV infection in children. The certainty of the evidence for most outcomes was moderate to high. Palivizumab reduces hospitalisation due to RSV infection (high certainty evidence) and probably results in a slight reduction in hospitalisation due to respiratory-related illness at two years' follow-up (moderate certainty evidence). Palivizumab probably results in little to no difference in mortality and adverse events and may result in little to no difference in length of hospital stay, days of supplemental oxygen, length of stay in the ICU, and mechanical ventilation days at 150 days' follow-up (low to moderate certainty evidence). Palivizumab may result in a large reduction in RSV infection at two years' follow-up (low certainty evidence). Palivizumab reduces the number of wheezing days at one year's follow-up (high certainty evidence).

Overall completeness and applicability of evidence

Participants in the included studies were similar to those that would be found in clinical practice, that is with a higher risk of severe RSV infection. The studies were conducted mainly in children and infants from six to 12 months old at the beginning of the RSV season. Two studies included participants with bronchopulmonary dysplasia and one study included participants with CHD, which might introduce a source of clinical heterogeneity. We deemed this not important for most outcomes. Most of the included studies delivered palivizumab intramuscularly, which is the current preferred route of administration (only one study delivered palivizumab intravenously).

Most studies reported all of the outcomes of interest in this review. We found heterogeneity in outcomes definitions amongst studies. Some outcomes reported hospitalisations under adverse events. Nevertheless, we were able to extract and analyse the available data accordingly.

Consistent with the 2013 Cochrane Review (Andabaka 2013), palivizumab reduced the risk for RSV-related hospitalisation, presenting similar statistical results. This conclusion reinforces the safety and efficacy of its use in high-risk children, in line with the different existing guidelines recommending its use (Brady 2014). Furthermore, these updated findings are of paramount significance in the context of the changing landscape of RSV

preventive interventions, including a new single-dose monoclonal antibody against RSV fusion protein (nirsevimab) that successfully diminished the incidence of RSV-associated lower respiratory tract infection episodes and hospitalisations (Griffin 2020).

Interestingly, we found that palivizumab resulted in a higher reduction in hospitalisation due to respiratory-related illness in LMIC than in HIC. This finding is aligned with the higher burden of RSV disease described in LMIC (Shi 2017). Moreover, a recent randomised clinical trial using a single intramuscular dose of RSV fusion protein nanoparticle vaccine in pregnant women showed a higher vaccine efficacy against RSV-associated lower respiratory tract infection in LMIC than in HIC (Madhi 2020). The effect of palivizumab on mortality was downgraded due to imprecision, which may also be due to the fact that the included studies were not from LMIC, and the overall mortality was low.

Palivizumab also resulted in a reduction in the number of wheezing days during the first year of life, in line with similar probe studies assessing this outcome (Yoshihara 2013). Being able to prevent recurrent wheezing is of great impact in preschoolers since it is one of the most frequent chronic pathologies in that age range (Stein 1999). Despite these encouraging results, in two follow-up studies, no differences in the diagnosis of asthma were seen at age six after the use of palivizumab (Mochizuki 2017; Scheltema 2018), although the effects of palivizumab on the subsequent diagnosis of asthma may be differ depending on the atopic status of the studied individuals (Simões 2010).

Quality of the evidence

The overall certainty of the evidence was moderate to high. Most outcomes reported in the studies were assessed as low risk of bias. A common problem found in several of the included studies was the incomplete reporting of dispersion measures that were not provided, leading us to calculate standard deviation converted from P values and thus making us less confident about the precision of the results. Some studies were very small and had few events which led to important imprecision. We were unable to assess publication bias due to the scarcity of studies per outcome.

Potential biases in the review process

We rearranged the mortality outcome to maximise the use of available data. We took precautions to avoid bias in this process by documenting all changes in the Differences between protocol and review section of the review. We found that several outcomes were reported in a subset of patients, such as hospitalised patients. As there were no data regarding all randomised participants in these cases, we decided to consider them as trials' exploratory analyses.

We followed the guidelines in Section 6.5 of the *CochraneHandbook* to obtain the standard deviation converted from P values (Higgins 2019c). We assumed a normal distribution of the available data. However, the probability of non-normal distribution of data remains, as no precise evidence of normal distribution could be found in the trial reports.

Agreements and disagreements with other studies or reviews

A previous Cochrane Review incorporating most of the studies included in our review found that palivizumab prophylaxis was effective in reducing the frequency of hospitalisations due to RSV infection and reducing the incidence of severe lower respiratory tract RSV disease in children with chronic lung disease, congenital heart disease or those born prematurely (Andabaka 2013). However, the comparators considered in Andabaka 2013 differed from those in our review.

A previous non-Cochrane systematic review included all of the studies in our review (Wegzyn 2014). Although our review did not include any new studies, we expanded the available knowledge related to the effect of palivizumab on different outcomes not considered in the previously mentioned review (Wegzyn 2014), such as the number of wheezing days. Furthermore, our review adds the risk of bias and certainty of the evidence assessments, which may be useful for decision-makers in the clinical setting and may also guide the design of future research.

One review found similar results regarding all-cause mortality and RSV hospitalisation amongst preterm infants at high risk (Checchia 2011); however, it included observational studies, both prospective and retrospective, and found mortality and hospitalisation rates lower than those found in our study. Another review found that prophylaxis with palivizumab reduced hospital admissions in preterm infants with or without chronic lung disease (Wang 2008). It also found that palivizumab reduced hospitalisation rate due to RSV amongst children with congenital heart disease. None of these non-Cochrane systematic reviews were of high quality, and none of them incorporated GRADE methods in assessing the certainty of the evidence.

We found additional systematic reviews and health technology assessments concluding that palivizumab is effective in reducing hospital stay and risk of admission in children with congenital heart disease (Harris 2011), prematurely born infants, infants with lung complications, and infants from remote communities (Mac 2019), but did not provide value for money because of its exceptionally high cost (Harris 2011). In this regard, a previous Cochrane Review found inconsistencies in palivizumab's cost-effectiveness, due to wide variations in incremental cost-effectiveness ratios (ICER), arising from different mortality rates, time horizons, and stakeholders' perspectives used in economic models (Andabaka 2013).

No previous review reported results for the number of wheezing days. This is a major issue, given the spreading hypothesis and studies suggesting that RSV infection is a risk factor for recurrent wheezing amongst infants and young children (Schauer 2002).

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence suggests that prophylaxis with palivizumab reduces hospitalisation due to respiratory syncytial virus (RSV) infection and results in little to no difference in mortality or adverse events. Moreover, palivizumab results in a slight reduction in hospitalisation due to respiratory-related illness and may result in a large reduction in severe RSV infections. Palivizumab also reduces the number of wheezing days. Despite our aim to determine the effect of palivizumab for preventing severe RSV infection in all children, no studies were found on healthy children without a higher risk for RSV life-threatening

disease or with immunodeficiency disorders, as all of the included studies were carried out in high-risk populations.

Implications for research

Further research is needed to establish the effect of palivizumab on children with other comorbidities known as risk factors for severe RSV disease (e.g. immune deficiencies) and other social determinants of the disease, including children living in low- and middle-income countries, tropical regions, children lacking breastfeeding, living in poverty, or members of families in overcrowded situations. Further research must consider the cost of the intervention in relation to the potential benefits arising from extended use and the subsequent impact on equity.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blanken 2013

Study characteristics	
Methods	Study design: prospective, randomised study. Study dates: April 2008 through December 2010 Setting: hospital, multicentre, national Country: the Netherlands

Blanken 2013 *(Continued)*

Participants	Inclusion criteria: • Healthy preterm infants • Gestational age between 32 and 35 weeks, either sex • Children of parents with mastery of the Dutch language Exclusion criteria: • A known cardiac anomaly, Down's syndrome or other serious congenital disorders • Require intensive respiratory treatment, defined as surfactant treatment or at least 2 weeks of mechanical ventilation • Greater than 6 months of age at the start of the RSV season, defined as 1st October of the year of birth • Airway morbidity before the start of the RSV season, monitored before the first injection. Total number of participants randomised: 429 Group 1: n = 214 palivizumab Male, n (%): 125 (58%) Birth weight, grams (95% CI): 2294 (1363 to 3325) Gestational age, weeks (95% CI) 34+3 (32+2-35+6) Multiple birth, n (%): 38 (19%) Type of feeding, n (%): Breastfeeding and formula: 90 (44%) Breastfeeding: 59 (29%) Formula: 54 (27%) Maternal smoking during pregnancy, n (%) 32 (15%) Parental smoking, n (%): Mother (%) 33 (15%) Father (%) 57 (27%) Siblings (%) 82 (44%) Age mother, median (range): 31 (19 to 48) Age father, median (range): 34 (21 to 55) Atopy mother, n (%): 85 (40%) Physician diagnosis (mother) asthma, n (%): 22 (11%) Physician diagnosis (mother) hay fever, n (%): 48 (24%) Physician diagnosis (mother) eczema, n (%): 48 (24%) Atopy father, n (%): 73 (34%) Physician diagnosis (father) asthma, n (%): 27 (14%) Physician diagnosis (father) hay fever, n (%): 44 (22%) Physician diagnosis (father) eczema, n (%): 29 (15%) Household pets, n (%): 97 (48%)

Blanken 2013 *(Continued)*

	Daycare attendance, n (%): 103 (48%) Sibling attending daycare, n (%): 75 (37%) Doses palivizumab received, median(range): 4 (1 to 5) Group 2: n = 215 placebo Male, n (%): 94 (44%) Birth weight, grams (95% CI): 2289 (1385 to 3358) Gestational age, weeks (95% CI): 34 + 3 (32 + 3 to 35 + 6) Multiple births, n (%): 36 (18%) Type of feeding, n (%): Breastfeeding and formula: 107 (53%) Breastfeeding: 49 (24%) Formula: 46 (23%) Maternal smoking during pregnancy, n (%): 34 (16%) Parental smoking, n (%): Mother (%): 36 (17%) Father (%): 62 (29%) Siblings (%): 85 (45%) Age mother, median (range): 32 (18 to 44) Age father, median (range): 35 (22 to 52) Atopy mother, n (%): 72 (34%) Physician diagnosis (mother) asthma, n (%): 24 (12%) Physician diagnosis (mother) hay fever, n (%): 45 (23%) Physician diagnosis (mother) eczema, n (%): 30 (15%) Atopy father, n (%): 80 (37%) Physician diagnosis (father) asthma, n (%): 21 (11%) Physician diagnosis (father) hay fever, n(%): 52 (26%) Physician diagnosis (father) eczema, n (%): 27 (14%) Household pets, n (%): 98 (49%) Daycare attendance, n (%): 113 (53%) Sibling attending daycare, n (%): 79 (40%) Doses palivizumab received, median (range): 4 (2 to 5)
Interventions	Group 1 (n = 214) palivizumab Interventions were intramuscular injections of palivizumab 15 mg/kg or placebo during 1 RSV season from 1 October or from discharge from the neonatal unit until 10 March. A minimum of 2 and a maximum of 5 injections were given. The RSV season was defined as running from 1 October through 31

Blanken 2013 *(Continued)*

	March based on virological data obtained from the National Institute of Public Health and the Environment (RIVM). Group 2 (n = 215) placebo: placebo was intramuscular injection of physiological sodium chloride 0.9% solution. Treatment was started at the child's home from the first week of October or within 72 hours after discharge from the neonatal hospitalisation. Co-interventions: All injections were administered at the child's home, and home visits ended after the last injection.
Outcomes	**Hospitalisation due to respiratory-related illness** How measured: children hospitalised with other respiratory tract illnesses (not RSV). Time points measured: 1 year Time points reported: 1 year Subgroups: none Group 1, n (%): 6 (2.8%) Group 2, n (%): 6 (2.8%) **Mortality** How measured: not reported Time points measured: throughout trial Time points reported: throughout trial Subgroups: none “There were no deaths” **Hospitalisation due to RSV infection** How measured: not reported Time points measured: 1 year Time points reported: 1 year Subgroups: none Group 1 (n = 214) palivizumab 1 year, n (%): 2 (0.9) Group 2 (n = 215) placebo 1 year, n (%): 11 (5.1) **RSV infection** How measured: parents were instructed to take a nasopharyngeal swab in case of the occurrence of respiratory symptoms with involvement of the upper or lower respiratory tract lasting more than 1 day. The swab was transported in a viral transport medium by regular mail to the laboratory and stored at −80 °C until PCR assays were performed. The presence of RSV RNA was determined by multiplex real-time reverse-transcriptase–PCR with the use of previously published primers and probes for RSV-B21 and primers and probes for RSV-A that were developed in-house. Time points measured: 1 year Time points reported: 1 year

Blanken 2013 *(Continued)*

Subgroups: none

Group 1 (n = 214) palivizumab

1 year, n (%): 10 (4.7)

Group 2 (n = 215) placebo

1 year, n (%): 30 (14.0)

Number of wheezing days

How measured: number of parent-reported wheezing days in the first year of life. Parents recorded airway symptoms, doctor visits, and the use of airway drugs in a daily log until infant was 1 year of age. Instructions for completing the log were given during the first home visit, and compliance was checked at each subsequent home visit.

Time points measured: 1 year

Time points reported: 1 year

Subgroups: none

Group 1 (n = 214) palivizumab

1 year:

Total log days (n): 53,075

Total symptoms days (n): 930

Incidence per day(%): 1.8

(Incidence of wheezing was calculated as the number of days with parent-reported airway symptoms divided by the number of log days during follow-up)

P < 0.001 for all comparisons

From Scheltema 2018:

Current use of asthma medication at 3 years follow-up: 14 (7.6%) (n = 184)

Use of asthma medication in the past 12 months at 6 years follow up:18 (9·0%) (n = 199)

Group 2 (n = 215) placebo

1 year:

Total log days (n): 51,726

Total symptoms days (n): 2309

Incidence per day (%): 4.5

*Incidence of wheezing was calculated as the number of days with parent-reported airway symptoms divided by the number of log days during follow-up

P < 0.001 for all comparisons

From Scheltema 2018:

Current use of asthma medication at 3 years follow-up: 23 (12.2%) of 188

Use of asthma medication in the past 12 months at 6 years follow up:25 (12.8%) (n = 195)

Notes	Funding sources: Abbott International PLC (UK) - no restrictions on publication of the research data.

Blanken 2013 *(Continued)*

The 2 study groups were well-balanced based on inclusion year, gestational age, and birth month. Birth weight, family history of atopy, presence of siblings, and other baseline characteristics were similar, except for sex (58% male infants in the RSV-prevention group versus 44% in the placebo group).

The study reported adverse events related to hospitalisations and deaths. We took account of this information in the relevant outcomes prespecified in the review.

Feltes 2003

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial. Study dates: during 4 RSV seasons, 1998 until 2002. Randomisation from 1 November until 31 December each year between 1998 and 2001. Setting: multicentre, multinational, outpatient Country: the study was conducted at 76 centres in the United States (47), Canada (6), Sweden (3), Germany (4), Poland (6), France (4) and the United Kingdom (6).
Participants	Inclusion criteria: • Children ≤ 24 months old at the time of randomisation with documented haemodynamically significant CHD determined by the investigator and had unoperated or partially corrected CHD Exclusion criteria: • Children with unstable cardiac or respiratory status, including cardiac defects so severe that survival was not expected or for which cardiac transplantation was planned or anticipated • Hospitalised children, unless discharge was anticipated within 21 days • Children with anticipated cardiac surgery within 2 weeks of randomisation • Children requiring mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other mechanical respiratory or cardiac support • Children with associated non-cardiac anomalies or end-organ dysfunction resulting in anticipated survival of < 6 months or unstable abnormalities of end-organ function • Known HIV infection • Acute RSV or other acute infection or illness • Previous receipt of palivizumab or other monoclonal antibody • Receipt of investigational agents within the previous 3 months (other than investigational agents commonly used during cardiac surgery or the immediate postoperative period, i.e. nitric oxide) • Current participation in other investigational protocols of drugs or biological agents • Receipt of intravenous immune globulin (IGIV), including RSV-IGIV (RespiGam, MedImmune, Inc, Gaithersburg, MD, USA), within 3 months before random assignment or anticipated use of IGIV, RSV-IGIV, or open-label palivizumab during the study period Sample size: 1287 participants Group 1 (n = 639): palivizumab Age (mean ± SE): 6.8 ± 0.2 months Sex n (%): male: 349 (54.6), female: 290 (45.4) Race/ethnicity, n (%): • White: 453 (70.9) • Hispanic: 77 (12.1)

Feltes 2003 *(Continued)*

- Black: 52 (8.1)
- Other: 57 (8.9)

Multiple birth, n (%): 27 (4.2)

Weight at entry (mean ± SE): 6.1 ± 0.1 kg

Gestational age (mean ± SE): 38.5 ± 0.1 weeks

RSV risk factors:

- Number of people in home (mean ± SE): 4.4 ± 0.1
- RSV neutralising antibody titre ≥ 1:200 at baseline, n (%): 170 (31.4)
- Child in daycare, n (%): 76 (11.9)
- Other children in daycare, n (%): 100 (15.6)
- Smoker in household, n (%): 211 (33.0)
- Family history of asthma, n (%): 172 (27.7)

Characteristics of CHD at study entry:

- Cyanotic stratum, n (%): 339 (53.1)
- Previous cardiac surgery or interventional catheterisation, n (%): 396 (62.0)
- Hypercyanotic episode, n (%): 73 (11.4)
- Receiving cardiac medications, n (%): 484 (75.7)
- Congestive heart failure, n (%): 401 (62.8)
- Pulmonary hypertension, n (%): 152 (23.8)
- Increased pulmonary blood flow, n (%): 237 (37.1)
- Children with cyanotic lesions, single ventricle including hypoplastic left or right heart and tetralogy of fallot, n (%): 140 (21.9)
- Children with acyanotic lesions, ventricular defect and atrioventricular defect, n (%): 115 (18.0)

Group 2 (n = 648): placebo

Age (mean ± SE): 6.5 ± 0.2 months

Sex n (%): male: 344 (53.1), female: 304 (46.9)

Race/ethnicity, n (%):

- White: 459 (70.8)
- Hispanic: 66 (10.2)
- Black: 61 (9.4)
- Other: 62 (9.6)

Multiple births, n (%): 23 (3.5)

Weight at entry (mean ± SE): 6.0 ± 0.1 kg

Gestational age (mean ± SE): 38.5 ± 0.1 weeks

RSV risk factors:

- Number of people in home (mean ± SE): 4.4 ± 0.1
- RSV neutralising antibody titre ≥ 1:200 at baseline, n (%): 173 (30.5)
- Child in daycare, n (%): 69 (10.6)
- Other children in daycare, n (%): 115 (17.7)
- Smoker in household, n (%): 223 (34.4)
- Family history of asthma, n (%): 191 (29.7)

Characteristics of CHD at study entry:

Feltes 2003 *(Continued)*

- Cyanotic stratum, n (%): 343 (52.9)
- Previous cardiac surgery or interventional catheterisation, n (%): 391 (60.3)
- Hypercyanotic episode, n (%): 84 (13.0)
- Receiving cardiac medications, n (%): 491 (75.8)
- Congestive heart failure, n (%): 428 (66.0)
- Pulmonary hypertension, n (%): 164 (25.3)
- Increased pulmonary blood flow, n (%): 253 (39.0)
- Children with cyanotic lesions, single ventricle including hypoplastic left or right heart and tetralogy of fallot, n (%): 74 (11.4)
- Children with acyanotic lesions, ventricular defect and atrioventricular defect, n (%): 47 (7.2)

Interventions	Group 1 (n = 639): palivizumab 15 mg/kg, intramuscular injection every 30 days for a total of 5 doses. Group 2 (n = 648): placebo (same formulation as palivizumab without antibody and with 0.02% Tween-80 added), intramuscular injection every 30 days for a total of 5 doses. Co-interventions: palivizumab and placebo were supplied as lyophillised product in coded vials that were reconstituted by the pharmacist with sterile water for injection (final concentration of palivizumab is 100 mg/mL) and dispensed in a syringe that did not identify the contents.
Outcomes	**Hospitalisation due to respiratory-related illness** How measured: number of children with cardiorespiratory hospitalisation, n (%) Time points measured: throughout the study Time points reported: throughout the study Group 1: 321 (50.2) Group 2: 359 (55.4) **Mortality** How measured: number of deaths (associated with RSV), n. Total number of deaths, n (%) Time points measured: throughout the study Time points reported: throughout the study Number of deaths (associated with RSV), n: Group 1: 2 Group 2: 4 Total number of deaths, n (%). Group 1: 21 (3.3) Group 2: 27 (4.2) (P = 0.463) **Adverse events** How measured: reported as total number of adverse events, total number of children (n) with adverse event (%), total number of children (n) with related adverse event, total number of children (n) with serious adverse event (%) and total number of children (n) with related serious event (%). Treatment groups were compared for adverse events (COSTART coded terms) by evaluating the number of children in each group with at least 1 event by body system and the distribution of severity and relatedness of these events. Any adverse change from a child's medical condition at entry was reported as an adverse event, graded for severity, and assessed by the blinded investigator as to potential relation to

Feltes 2003 *(Continued)*

study drug. Serious adverse events were those that resulted in death; were life-threatening; resulted in hospitalisation or prolonged hospitalisation; resulted in significant disability; or were another important medical event that required intervention to prevent 1 of the above outcomes.

Time points measured: children were followed for 150 days from random assignment (30 days after the last scheduled study injection) for the occurrence of adverse events.

Time points reported: children were followed for 150 days from random assignment (30 days after the last scheduled study injection) for the occurrence of adverse events.

Total number of adverse events, n:

Group 1: 4169

Group 2: 4518

Total number of children with adverse event, n (%):

Group 1: 611 (95.6)

Group 2: 625 (96.5)

(P = 0.477)

Total number of children with adverse event coding to cardiovascular system, n (%):

Group 1: 286 (44.8)

Group 2: 315 (48.6)

(P = 0.180)

Total number of children with adverse event coding to respiratory system, n (%):

Group 1: 525 (82.2)

Group 2: 547 (84.4)

(P = 0.296)

Total number of children with adverse event requiring medical intervention, n (%):

Group 1: 588 (92.0)

Group 2: 605 (93.4)

(P = 0.392)

Total number of children with related adverse event, n (%):

Group 1: 46 (7.2)

Group 2: 45 (6.9)

(P = 0.914)

Total number of children with related adverse event resulting in permanent discontinuation, n (%):

Group 1: 0 (0.0)

Group 2: 0 (0.0)

Total number of children with serious adverse event, n (%):

Group 1: 354 (55.4)

Group 2: 409 (63.1)

Feltes 2003 *(Continued)*

(P = 0.005)

Total number of children with related serious event, n (%):

Group 1: 0 (0.0)

Group 2: 3 (0.5)

(P = 0.249)

Subgroups:

Incidence of serious adverse of events, (%):

Group 1:

Cyanotic stratum: 59.9

"Other" stratum: 50.3

Group 2:

Cyanotic stratum: 67.1

"Other" stratum: 58.7

Days of supplemental oxygen

How measured: total RSV hospital days with increased oxygen requirement, n (total days per 100 children). Also reported as relative reduction (%).

Time points measured: throughout the study.

Time points reported: throughout the study.

Group 1: 178 (27.9)

Group 2: 658 (101.5)

Reduction: 73 (P = 0.014)

Intensive care unit length of stay

How measured: total days of RSV-associated intensive care, n (total days per 100 children). Also reported as relative reduction (%).

Time points measured: throughout the study.

Time points reported: throughout the study.

Group 1: 101 (15.9)

Group 2: 461 (71.2)

Reduction: 78

(P = 0.080)

Mechanical ventilation days

How measured: total days of RSV-associated mechanical ventilation, n (total days per 100 children). Also reported as relative reduction (%).

Time points measured: throughout the study

Time points reported: throughout the study

Group 1: 42 (6.5)

Feltes 2003 *(Continued)*

	Group 2: 354 (54.7) Reduction: 41 (P = 0.224) **Hospitalisation due to RSV infection** How measured: incidence of RSV hospitalisation, n (%). Also reported as total days of RSV hospitalisation, D (total days per 100 children). In addition, reported as relative reduction of RSV hospitalisation rate, % and relative reduction of total days of RSV hospitalisation, %. Time points measured: throughout the study Time points reported: throughout the study Group 1: 34 (5.3), D: 367 (57.4) Group 2: 63 (9.7), D: 836 (129.0) Reduction (rate): 45 Reduction (days): 56 (P = 0.003)
Notes	Overall, 93.0% of children in the palivizumab group and 91.8% in the placebo group received all 5 planned injections; 95.6% in the palivizumab group and 95.5% in the placebo group completed the study. No child had study drug discontinued for a related adverse event. A total of 48 children died during the study: 21 (3.3%) in the palivizumab group and 27 (4.2%) in the placebo group. No deaths were attributed to study drug. Deaths associated with RSV infection occurred in 2 children in the palivizumab group and 4 children in the placebo group.

IMpact-RSV Study Group 1998

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial, multicentre (139 sites), phase III trial. Study dates: randomisation from 15 November 1996 until 13 December 1996. Study executed during the 1996 to 1997 RSV season. Setting: multicentre, multinational, outpatient Country: the United States (110 centres), the United Kingdom (11 centres) and Canada (9 centres)
Participants	Inclusion criteria: • Children 35 weeks gestation or less and 6 months of age or younger • Children 24 months old or younger and had a clinical diagnosis of BPD requiring ongoing medical treatment Exclusion criteria: • Hospitalisation at the time of entry that was anticipated to last more than 30 days • Mechanical ventilation at the time of entry • Life expectancy less than 6 months • Active or recent RSV infection • Known hepatic or renal dysfunction • Seizure disorder

IMpact-RSV Study Group 1998 *(Continued)*

- Immunodeficiency
- Allergy to IgG products
- Receipt of RSV immune globulin within the past 3 months
- Previous receipt of palivizumab, other monoclonal antibodies, RSV vaccines or other investigational agents
- Children with congenital heart disease (if complicated and haemodynamically significant)

Sample size: 1502 children.

Group 1 (n = 500): placebo

Age (mean ± SE): 6.0 ± 0.21 months

Sex %: male: 56.8%, female:43.2%

Race/ethnicity (%):

- White: 57.4
- Black: 25.6
- Hispanic: 10.8
- Asian: 2.4
- Other: 3.8

Birth weight (mean ± SE): 1.3 ± 0.02 kg

Gestational age (mean ± SE):29 ± 0.14 weeks

Proportion of children with gestational age ≤ 32 weeks (%): 83.4

Proportion of children with gestational age > 32 weeks (%): 16.6

Multiple birth (%): 27.4

Weight at entry (mean ± SE): 4.9 ± 0.1 kg

Previous RSV (%): 1: 5.6

RSV neutralising antibody ≥ 1:200 (%): 5.6

Number of people in house (mean ± SE): 3.5 ± 0.07

Smoker in household (%):68.6

Child in daycare (%): 6.8

Family history of asthma (%): 35.2

Family history of hay fever (%): 29.6

Family history of eczema (%): 16.4

Premature children (no BPD), n (%): 234 (46.8)

Children with BPD, n (%): 266 (53.2)

Group 2 (n = 1002): palivizumab

Age (years): mean age at study entry (months ± SE): 5.7 ± 0.15

Sex %: male: 56.9%, female: 43.1%

Race/ethnicity (%):

- White: 58.4
- Black: 22.8

IMpact-RSV Study Group 1998 *(Continued)*

	• Hispanic: 11.0 • Asian: 2.1 • Other: 5.8 Birth weight (mean ± SE): 1.3 ± 0.02 kg Gestational age (mean ± SE): 29 ± 0.10 weeks Proportion of children with gestational age ≤ 32 weeks (%): 83.8 Proportion of children with gestational age > 32 weeks (%): 16.2 Multiple birth (%): 31.7 Weight at entry (mean ± SE): 4.8 ± 0.1 kg Previous RSV (%): 3.8 RSV neutralising antibody ≥ 1:200 (%): 5.5 Number of people in house (mean ± SE): 3.5 ± 0.05 Smoker in household (%): 63.0 Child in daycare (%): 6.7 Family history of asthma (%): 36.1 Family history of hay fever (%): 28.6 Family history of eczema (%): 16.5 Premature children (no BPD), n (%): 506 (50.5) Children with BPD, n (%): 496 (49.5)
Interventions	Group 1 (n = 500): placebo (same formulation as group 2 but without antibody and with 0.02% Tween-80 added), intramuscular injection every 30 days, 5 doses. Group 2 (n = 1002): palivizumab 15 mg/kg (concentration 100 mg/mL), intramuscular injection every 30 days, 5 doses
Outcomes	**Hospitalisation due to respiratory-related illness** How measured: incidence of respiratory hospitalisations, %, and incidence of respiratory hospitalisations unrelated to RSV (%). Time points measured: throughout the study Time points reported: throughout the study Incidence of respiratory hospitalisations (%): Group 1: 22 Group 2: 16 (P = 0.008) Incidence of respiratory hospitalisations unrelated to RSV (%) Group 1: 14 Group 2: 13 (P = 0.470)

IMpact-RSV Study Group 1998 *(Continued)*

Mortality

How measured: number of deaths, n (%). (Cause of death not specified)

Time points measured: throughout the study

Time points reported: throughout the study

Group 1: 5 (1.0)

Group 2: 4 (0.4)

Adverse events

How measured: number of children (n) and proportion of children (%) reporting adverse events judged by the blinded investigator to be related to the study drug. Adverse events were assessed by the investigators with regard to severity (using a standard toxicity table modified from the Pediatric AIDS Clinical Trials Group) and potential relationship to the study drug. Treatment groups were compared for adverse events by evaluating the number of children in each group with at least 1 event by body system and the distribution of severity of these events.

Time points measured: 150 days from randomisation (30 days after last scheduled injection).

Time points reported: throughout the study period.

Group 1: 50 (10)

Group 2: 110 (11)

Number of children reporting adverse events related to the injection site, n (%)

Group 1: 9 (1.8)

Group 2: 27 (2.7)

Erythema, n (%):

Group 1: 6 (1.2)

Group 2: 14 (1.4)

Pain, n (%):

Group 1: 0 (0.0)

Group 2: 6 (0.6)

Induration/swelling, n (%):

Group 1: 1 (0.2)

Group 2: 6 (0.6)

Bruising, n (%):

Group 1: 2 (0.4)

Group 2: 3 (0.3)

Most frequently reported adverse events that were judged by the blinded investigator as potentially related to study drug, n (%).

Fever:

Group 1: 15 (3.0)

Group 2: 28 (2.8)

IMpact-RSV Study Group 1998 *(Continued)*

(P = 0.870)

Nervousness:

Group 1: 13 (2.6)

Group 2: 25 (2.5)

(P = 0.865)

Injection site reaction:

Group 1: 8 (1.6)

Group 2: 23 (2.3)

(P = 0.444)

Diarrhoea:

Group 1: 2 (0.4)

Group 2: 10 (1.0)

(P = 0.357)

Rash:

Group 1: 1 (0.2)

Group 2: 9 (0.9)

(P = 0.179)

AST increased:

Group 1: 3 (0.6)

Group 2: 5 (0.5)

(P = 0.726)

Upper respiratory tract illness:

Group 1: 2 (0.4)

Group 2: 5 (0.5)

(P = 1.000)

Liver function abnormal (primarily elevations of both AST and ALT):

Group 1: 1 (0.2)

Group 2: 3 (0.3)

(P = 1.000)

ALT increased:

Group 1: 2 (0.4)

Group 2: 3 (0.3)

(P = 0.670)

Vomiting:

IMpact-RSV Study Group 1998 *(Continued)*

Group 1: 2 (0.4)

Group 2: 3 (0.3)

(P = 0.670)

Cough:

Group 1: 1 (0.2)

Group 2: 3 (0.3)

(P = 1.000)

Rhinitis:

Group 1: 3 (0.6)

Group 2: 3 (0.3)

(P = 0.406)

Children with mild or moderate elevations of AST (measured at baseline and before the fourth injection), n (%):

Group 1: 8 (1.6)

Group 2: 36 (3.6)

Children with mild or moderate elevations of ALT (measured at baseline and before the fourth injection), n (%):

Group 1: 10 (2.0)

Group 2: 23 (2.3)

Length of hospital stay

How measured: total days of all hospitalisations per 100 children, total days of respiratory hospitalisations per 100 children and total days of respiratory hospitalisations unrelated to RSV per 100 children

Time points measured: throughout the study.

Time points reported: throughout the study.

Total days of all hospitalisations per 100 children:

Group 1: 242

Group 2: 191

(P = 0.005)

Total days of respiratory hospitalisations per 100 children:

Group 1: 180

Group 2: 124

(P = 0.004)

Total days of respiratory hospitalisations unrelated to RSV per 100 children:

Group 1: 118

Group 2: 88

(P = 0.369)

IMpact-RSV Study Group 1998 *(Continued)*

Days of supplemental oxygen

How measured: number of days in RSV hospitalisation with increased oxygen, n:

Time points measured: throughout the study

Time points reported: throughout the study

Group 1: 50.6
Group 2: 30.3

(P < 0.001)

Intensive care unit length of stay

How measured: total days of RSV ICU admissions, n, and incidence of RSV ICU admissions (%)

Time points measured: throughout the study

Time points reported: throughout the study

Group 1: 12.7 (3.0)
Group 2: 13.3 (1.3)

(n: P = 0.023, %: P = 0.026)

Mechanical ventilation days

How measured: total days, n, and incidence of mechanical ventilation (%) during RSV hospitalisation

Time points measured: throughout the study

Time points reported: throughout the study

Group 1: 1.7 (0.2)

Group 2: 8.4 (0.7)

(n: P = 0.210, %: P = 0.280)

Hospitalisation due to RSV infection

How measured: total days of RSV hospitalisation per 100 children (D) and incidence of RSV hospitalisation, n (%). Also reported as reduction in hospitalisation as a result of RSV, % (95% CI).

Time points measured: throughout the study

Time points reported: throughout the study

Total days of RSV hospitalisation per 100 children:

Group 1: 62.6

Group 2: 36.4

(P < 0.001)

Reduction: 55 (38 to 72)

Incidence of RSV hospitalisation, n (%)

Group 1: 53 (10.6)

Group 2: 48 (4.8)

(P < 0.001)

Reduction: 55 (38 to 72)

IMpact-RSV Study Group 1998 *(Continued)*

	Subgroups: Number of RSV hospitalisations, n (%). Group 1: Premature (no BPD): 19 (8.1) BPD: 34 (12.8) Group 2: Premature (no BPD): 9 (1.8) BPD: 39 (7.9) Reduction in RSV hospitalisations, %: Infants > 5 kg: 51 Infants ≤ 5 kg: 57 Infants < 32 weeks gestational age: 47 Infants 32-25 weeks gestational age: 80
Notes	A total of 1486 (99%) children completed the protocol follow-up (99% placebo, 99% palivizumab). Reasons for non-completion included death, not judged as a result of palivizumab, (n = 7), withdrawal of consent (n = 4); or loss to follow-up (n = 5) before day 150 and before any RSV hospitalisation. Overall, 94% of the placebo group and 92% of the palivizumab group received all 5 injections and more than 95% of both groups received at least 4 injections. Discontinuation of injections due to adverse events related to palivizumab was rare (0.3%).

Subramanian 1998

Study characteristics	
Methods	Study design: phase I/II multicentre (10 sites), randomised, double-blind, placebo-controlled, dose escalation trial. Study dates: randomisation from 27 November 1995 until 15 February 1996. Infusions completed by 19 April 1996. Setting: multicentre, national, outpatient. Country: the United States.
Participants	Inclusion criteria: • Infants born at 35 weeks gestation or less and <= 6 months of age • Infants with BPD and <= 24 months of age Exclusion criteria: • Mechanical ventilation at the time of enrolment • Life expectancy < 1 year • Known renal impairment, hepatic dysfunction, persistent seizure disorder or immunodeficiency • BUN, creatinine, AST, ALT or bilirubin > 1.5 times the upper limit of normal for age • Haemoglobin < 9.0 g/dL • White blood cell count < 2000 cells/mm^3

Subramanian 1998 *(Continued)*

- Platelet count < 110 000 cells/mm^3
- Abnormal serum IgG, IgM and IgA values, positive hepatitis B surface antigen, hepatitis C antibody, or HIV antibody (unless proved not to be infected with HIV)
- Supplemental oxygen requirement of > 30% FiO_2 or > 1.5 L/min
- Any acute illness or progressive clinical disorder, including acute RSV infection
- Previous reaction to intravenous immunoglobulin, blood products, or other foreign proteins
- Treatment with intravenous immunoglobulin or other immunoglobulin products within the past 2 months
- Treatment with other investigational agents or participation in any investigational study of RSV agents
- Expectation that the child would not be able to be followed for the duration of the study

Sample size: 62 infants were randomised. 57 participants completed the study (received a study drug).

Group 1 (n = 20): placebo. 0.9% saline intravenously every 30 days for up to 5 doses

Age at study entry (mean ± SE): 5.0 ± 0.83 months

Sex (M/F): not available.

Relevant participant details:

- Children in BPD category, n (%): 16 (80.0)
- Children in premature category, n (%): 4 (20.0)
- Weight at entry (mean ± SE): 3768.9 ± 509.26 g
- Children with gestational age ≤ 32 weeks, n (%): 20 (100.0)
- Children with 1 to 2 previous hospitalisations, n (%): 12 (60.0)
- Children with > 2 previous hospitalisations, n (%): 0 (0.0)
- Children with unknown previous hospitalisations, n (%): 8 (40.0)
- Children with previous RSV infection, n (%): 2 (10.0)
- Children with previous LRI, n (%): 9 (45.0)
- Entry LRI score (mean ± SE): 0.8 ± 0.24

Group 2 (n = 10): 3 mg/kg MEDI-493 intravenously every 30 days for up to 5 doses

Age at study entry (mean ± SE): 6.9 ± 1.28 months

Sex (M/F): not available

Relevant participant details:

- Children in BPD category, n (%): 10 (100.0)
- Children in premature category, n (%): 0 (0.0)
- Weight at entry (mean ± SE): 5234.8 ± 831.18 g
- Children with gestational age ≤ 32 weeks, n (%): 10 (100.0)
- Children with 1 to 2 previous hospitalisations, n (%): 8 (80.0)
- Children with > 2 previous hospitalisations (%): 0 (0.0)
- Children with unknown previous hospitalisations, n (%): 2 (20.0)
- Children with previous RSV infection, n (%): 0 (0.0)
- Children with previous LRI, n (%): 2 (20.0)
- Entry LRI score (mean ± SE): 0.6 ± 0.27

Group 3 (n = 10): 10 mg/kg MEDI-493 intravenously every 30 days for up to 5 doses

Age at study entry (mean ± SE): 7.3 ± 2.01 months

Sex (M/F): not available.

Relevant participant details:

Subramanian 1998 *(Continued)*

- Children in BPD category, n (%): 8 (80.0)
- Children in premature category, n (%): 2 (20.0)
- Weight at entry (Mean ± SE): 5413.4 ± 886.01 g
- Children with gestational age ≤ 32 weeks, n (%): 8 (80.0)
- Children with 1 to 2 previous hospitalisations, n (%): 6 (60.0)
- Children with > 2 previous hospitalisations, n (%): 3 (30.0)
- Children with unknown previous hospitalisations, n (%):1 (10.0)
- Children with previous RSV infection, n (%): 3 (30.0)
- Children with previous LRI, n (%): 4 (40.0)
- Entry LRI score (mean ± SE): 0.6 ± 0.27

Group 4 (n = 22): 15 mg/kg MEDI-493 intravenously every 30 days for up to 5 doses

Age at study entry (mean ± SE): 8.1 ± 1.69 months

Sex (M/F): not available

Relevant participant details:

- Children in BPD category, n (%): 18 (81.8)
- Children in premature category, n (%): 4 (18.2)
- Weight at entry (mean ± SE): 4888.6 ± 738.73 g
- Children with gestational age ≤ 32 weeks, n (%): 20 (90.9)
- Children with 1 to 2 previous hospitalisations, n (%): 12 (54.5)
- Children with > 2 previous hospitalisations, n (%): 3 (13.6)
- Children with unknown previous hospitalisations, n (%): 7 (31.8)
- Children with previous RSV infection, n (%): 1 (4.5)
- Children with previous LRI, n (%): 7 (31.8)
- Entry LRI score (mean ± SE): 0.7 ± 0.20

Interventions	Group 1 (n = 20): placebo. 0.9% saline intravenously every 30 days for up to 5 doses. Group 2 (n = 10): 3 mg/kg MEDI-493 intravenously every 30 days for up to 5 doses. Group 3 (n = 10): 10 mg/kg MEDI-493 intravenously every 30 days for up to 5 doses. Group 4 (n = 22): 15 mg/kg MEDI-493 intravenously every 30 days for up to 5 doses. For groups 2, 3 and 4: MEDI-493 was formulated in phosphate-buffered saline without preservatives; 10 mg/mL, 10 mL/vial, pH 7.4. For administration MEDI-493 was withdrawn from the vial using a syringe and 0.2-µm pore size filter. The volume of study drug was calculated based on the child's weight (rounded to the nearest 0.1 kg) on the day of the visit. For groups 3 and 4: dosing was initiated at 3 mg/kg; escalations to 10 mg/kg and finally to 15 mg/kg were based on cumulative safety data from the preceding dosages. Co-interventions: infusions were given in 2 to 5 min using standard intravenously infusion equipment.
Outcomes	**Hospitalisation due to respiratory-related illness** How measured: number of occurrences (O) and number of children hospitalised due to any respiratory infection, n (%). Time points measured: throughout the study. Time points reported: throughout the study. Group 1: (O: 4), 3 (15.0) Group 2: (O: 5), 5 (50.0)

Subramanian 1998 *(Continued)*

Group 3: (O: 1), 1 (10.0)

Group 4: (O: 4), 3 (13.6)

Mortality

How measured: number of deaths, n (%) (not due to RSV infection)

Time points measured: throughout the study

Time points reported: throughout the study

Group 1: 1 (5.0) (disseminated adenovirus infection)

Group 2: 0 (0.0)

Group 3: 0 (0.0)

Group 4: 0 (0.0)

Adverse events

How measured: number of children that experienced adverse events judged as potentially related to study drug, n (%). Adverse events were graded for severity (mild, moderate, severe and life-threatening) using a toxicity table (modified from the AIDS Clinical Trials Group paediatric toxicity tables). All adverse events were assessed by the blinded investigator as to potential relationship to study drug (none, remote, possible, probably or definitely related). Any adverse event graded as greater than moderate, as well as any fatal, life-threatening or permanently disabling events and any inpatient hospitalisations, prolonged hospitalisations or overdoses were classified as serious adverse events. Adverse events were coded by body system using a standard COSTART adverse event dictionary. For analytical purposes the total numbers of infants in each dose group reporting 1 or more adverse events in each body system were compared. MEDI-493 groups were compared with the pooled placebo group.

Time points measured: adverse events were reported through 30 days after the last infusion visit.

Time points reported: adverse events were reported through 30 days after the last infusion visit.

Group 1: 3 (15)
Group 2: 1 (10)
Group 3: 0 (0)
Group 4: 5 (23)

Total number of adverse events judged potentially related to study drug reported by all participants: n = 14

Most frequent events reported by all participants, n:

Fever: 3

Right upper lobe pneumonia: 2

Infusion site infiltration: 2

Increased transaminase values, n (%):

Group 1: 1 (5)
Group 2: 0 (0)
Group 3: 1 (10)
Group 4: 2 (9.1)

RSV infection

How measured: number of occurrences (O) and number of children with RSV respiratory illness, n (%). Measured with RSV antigen tests (and RSV cultures for some children).

Time points measured: throughout the study.

Subramanian 1998 *(Continued)*

Time points reported: throughout the study.

Group 1: (O: 4), 4 (20.0)

Group 2: (O: 3), 3 (30.0)

Group 3: (O: 1), 1 (10.0)

Group 4: (O: 2), 2 (9.1)

Hospitalisation due to RSV infection

How measured: number of occurrences (O) and number of children with RSV respiratory illness hospitalisation, n (%).

Time points measured: throughout the study.

Time points reported: throughout the study.

Group 1: (O: 2), 2 (10.0)

Group 2: (O: 2), 2 (20.0)

Group 3: (O: 0), 0 (0.0)

Group 4: (O: 0), 0 (0.0)

Notes	1 child was randomised to placebo but inadvertently received 15 mg/kg MEDI-493 and was analysed as a 15 mg/kg MEDI-493 patient. Overall 57 (91.9%) children completed the study. Reasons for premature termination included withdrawal of consent (4 children) and death (1 placebo patient). Only 4 children (6.5%) received fewer than 3 infusions (3 withdrawal of consent, 1 iv infiltration). No infants withdrew because of an adverse event. All of the study drug was administered in 96.2% of attempted infusions; incomplete infusions were the result of technical difficulties with the intravenous infusion. The intervention arms with a lower dose of palivizumab were not included in our analysis.

Tavsu 2014

Study characteristics	
Methods	Study design: prospective, randomised study. Study dates: 2 RSV seasons (October to March, 2009 to 2010 and 2010 to 2011) Setting: inpatient, single centre, national Country: Turkey
Participants	Inclusion criteria: • Infants born before the gestational age of 32 weeks • Hospitalised in the neonatal intensive care unit • Infants born at 28 week gestational age who were younger than 12 mo old at the beginning of RSV season • Infants born at 29 to 32 week gestational age who were younger than 6 months old at the beginning of RSV season. Exclusion criteria: • Chronic lung disease • Congenital heart disease

Tavsu 2014 *(Continued)*

	• Any other serious problems (intraventricular haemorrhage, retinopathy, hearing problems, etc.) apart from prematurity Total number of participants randomised: 83 Group 1: n = 41 palivizumab Gestational age, mean (SD): 29.4 (1.8) weeks Birth weight, mean (SD): 1317 (255) g Cesarean delivery, n (%): 35 (89.7) Female, n (%) 19 (48.7) Infants on mechanical ventilator, n (%): 30 (76.9) Respiratory distress syndrome, n (%): 30 (76.9) Days of hospitalisation, median (IQR): 35 (21 to 52) days Group 2: n = 42 no intervention Gestational age, mean (SD): 29.7 (1.6) weeks Birth weight, mean (SD): 1404 (270) g Cesarean delivery, n (%): 34 (82.9) Female, n (%): 24 (58.5) Infants on mechanical ventilator, n (%): 27 (65.9) Respiratory distress syndrome, n (%): 27 (65.9) Days of hospitalisation, median (IQR): 27 (19 to 46) days
Interventions	Group 1 (n = 39) palivizumab: study group received prophylaxis with palivizumab for the prevention of RSV infection monthly for 1 season (15 mg/kg/dose, 5 doses between October and March). Group 2 (n = 41) no intervention: control group did not receive palivizumab prophylaxis. Co-interventions: not reported. Both groups were followed up during 2 RSV seasons (2009 to 2010 and 2010 to 2011).
Outcomes	**Hospitalisation due to respiratory-related illness** How measured: infants were hospitalised if they had severe respiratory distress, intercostal retractions, cyanosis, and feeding intolerance with or without fever. In all hospitalised cases the test was performed within the first 48 hours of hospitalisation. If RSV was not present, the attack was denoted as non-RSV infection. Time points measured: 1 and 2 years follow-up Time points reported: 1 and 2 years follow-up Subgroups: none Group 1 (n = 39) palivizumab 1-year follow-up, n (%): 1 (2.6) 2 year follow-up, n (%): 5 (12.8)

Tavsu 2014 *(Continued)*

Group 2 (n = 41) no intervention

1-year follow-up, n (%): 2 (4.8)

2 year follow-up, n (%): 1 (2.4)

Mortality

How measured: not reported

Time points measured: 1 and 2 year follow-up

Time points reported: 1 and 2 year follow-up

Subgroups: none

"No infants died during follow-up."

Hospitalisation due to RSV infection

How measured: Infants were hospitalised if they had severe respiratory distress, intercostal retractions, cyanosis, and feeding intolerance with or without fever. In all hospitalised cases the test was performed within the first 48 hours of hospitalisation. If RSV was not present, the attack was denoted as non-RSV infection.

Time points measured: 1 and 2 year follow-up

Time points reported: 1 and 2 year follow-up

Subgroups: none

Group 1 (n = 39) palivizumab

1 year follow-up, n (%): 0

2 year follow-up, n(%): 0

Group 2 (n = 41) no intervention

1 year follow-up, n (%): 10 (24.4)

2 year follow-up, n (%): 10 (24.4)

RSV infection

How measured: Respi-Strips (Coris BioConcept, Gembloux, Belgium) test was used for the detection of RSV (Coris BioConcept). For this purpose, a nasal swab was obtained and mixed in 0.5 mL of normal saline. Around 0.25 mL (8 drops) of this solution was mixed with 0.25 mL of test solution and 10 minutes later the test strip was inserted into the solution. A single line in the test strip was regarded as negative and 2 lines were regarded as positive for RSV. If the test was positive for RSV, but the infant had no symptom of respiratory illness, this infant was denoted as RSV (+)

Time points measured: 1 year and 2 years follow-up

Time points reported: 1 year and 2 years follow-up

Subgroups: none

Group 1 (n = 39) palivizumab

1 year follow-up, n (%): 11 (28.2)

LRTI due to RSV (1 year):9 (23.1)

2 years follow-up, n (%): 14 (35.9)

LRTI due to RSV (2 years): 6 (15.4)

Tavsu 2014 *(Continued)*

	Group 2 (n = 41) no intervention 1-year follow-up, n (%): 24 (58.5) LRTI due to RSV (1 year): 22 (53.7) 2 years follow-up, n (%): 22 (53.7) LRTI due to RSV (2 years): 20 (48.8)
Notes	A total of 41 infants were randomised to the study group and 42 infants to the control group. 2 infants from the study group and 1 infant from the control group dropped out of the study.

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BPD: bronchopulmonary dysplasia
BUN: blood urea nitrogen
CHD: congenital heart disease
CI: confidence interval
COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms
FiO_2: fraction of inspired oxygen
ICU: intensive care unit
IgA: immunoglobulin A
IgG: immunoglobulin G
IgM: immunoglobulin M
IQR: interquartile range
LRI: lower respiratory infection
LRTI: lower respiratory tract infection
PCR: polymerase chain reaction
RNA: ribonucleic acid
RSV: respiratory syncytial virus
SD: standard deviation
SE: standard error

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 1999	Wrong study design. Commentary on palivizumab
Anonymous 2004	No full text available: possibly a narrative review or comment.
Driver 1999	Wrong study design. Narrative review of available evidence related to palivizumab
EUCTR2007-002070-61-PL	Wrong comparator. Ongoing trial comparing palivizumab against motavizumab
Ignacio 2013	Wrong study design. Commentary on Blanken 2013
Johnson 1999	Wrong study design. No full text available. Probably a narrative review or comment
Koganesawa 2019	Wrong study design. Case series of patients with immunodeficiencies receiving palivizumab
Naver 2002	Wrong study design. Commentary on palivizumab
Pin 2002	Wrong study design. Narrative review on palivizumab
Rajakumar 2009	Wrong study design. A retrospective descriptive study of children receiving palivizumab

Study	Reason for exclusion
Tulloh 2011	Wrong study design. A cohort study of children who underwent cardiac surgery and where included previously in Feltes 2003

Characteristics of studies awaiting classification *[ordered by study ID]*

EUCTR 2018-002980-25-IT

Methods	Parallel group, randomised, multicentre, open-label study
Participants	Newborns until 6 months of age
Interventions	Palivizumab (dosage not reported) versus placebo
Outcomes	**Primary outcomes** Overall respiratory morbidity (composite primary endpoint), whose definition is: - LRTIs by any pathogen (including, but not limited to, RSV) + - recurrent wheezing (quantified as the presence of wheezing days and/or need for use of anti-wheezing drugs) +/- asthma **Secondary outcomes** Difference of RSV-related hospitalisation due to LRTI during the first RSV-season (November 1st to March 31th) between Group A (treated with palivizumab) and Group B (not treated). Direct costs in terms of difference of health resources used by Group A and Group B respectively and related to: - length of hospitalisations (days); - mechanical ventilation and other support therapies (type, number, duration); - ICU admission and length of stay (days); - outpatient visits (type and number of specialistic visits); - drugs (type, dosages and therapy duration); and - diagnostic tests (type and number). Costs for resources used will be calculated using National Health Service tariffs. Indirect costs in terms of loss of working days for parents due to child illness.
Notes	Insufficient information on the trial record to determine inclusion as an ongoing trial.

Lenney 1998

Methods	Not available
Participants	Not available
Interventions	Not available
Outcomes	Not available
Notes	Full text not available. Possibly a secondary report of IMpact-RSV Study Group 1998.

ICU: intensive care unit
LRTI: lower respiratory tract infection
RSV: respiratory syncytial virus

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 Hospitalisation due to RSV infection

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Blanken 2013	✓	✓	✓	✓	✓	✓
Feltes 2003	✓	✓	✓	✓	✓	✓
IMpact-RSV Study Group 1998	✓	✓	✓	✓	✓	✓
Subramanian 1998	✓	✓	✓	✓	✓	✓
Tavsu 2014	~	~	✓	✓	✓	~

Risk of bias for analysis 1.2 Mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Blanken 2013	✓	✓	✓	✓	✓	✓
Feltes 2003	✓	✓	✓	✓	✓	✓
IMpact-RSV Study Group 1998	✓	✓	✓	✓	✓	✓
Subramanian 1998	✓	✓	✓	✓	✓	✓
Tavsu 2014	~	~	✓	✓	✓	~

Risk of bias for analysis 1.3 Adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Feltes 2003	✓	✓	✓	✓	✓	✓
IMpact-RSV Study Group 1998	✓	✓	✓	✓	✓	✓
Subramanian 1998	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Hospitalisation due to respiratory-related illness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Blanken 2013	✓	✓	✓	✓	✓	✓
Feltes 2003	✓	✓	✓	✓	✓	✓
IMpact-RSV Study Group 1998	✓	✓	✓	✓	✓	✓
Subramanian 1998	✓	✓	✓	✓	✓	✓
Tavsu 2014	~	~	✓	✓	✓	~

Risk of bias for analysis 1.5 Subgroup analysis: hospitalisation due to respiratory-related illness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 High-income countries						
Blanken 2013	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Feltes 2003	✓	✓	✓	✓	✓	✓
IMpact-RSV Study Group 1998	✓	✓	✓	✓	✓	✓
Subramanian 1998	✓	✓	✓	✓	✓	✓
Subgroup 1.5.2 Low- and middle-income countries						
Tavsu 2014	~	~	✓	✓	✓	~

Risk of bias for analysis 1.7 RSV infection

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Blanken 2013	✓	✓	✓	✓	✓	✓
Subramanian 1998	✓	✓	✓	✓	✓	✓
Tavsu 2014	~	~	✓	✓	✓	~

Risk of bias for analysis 1.8 Number of wheezing days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Blanken 2013	✓	✓	✓	✓	✓	✓

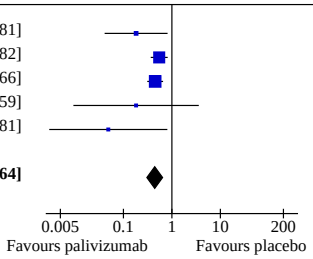
DATA AND ANALYSES

Comparison 1. Palivizumab versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Hospitalisation due to RSV infection	5	3343	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.30, 0.64]
1.2 Mortality	5	3343	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.42, 1.15]
1.3 Adverse events	3	2831	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.85, 1.39]
1.4 Hospitalisation due to respiratory-related illness	5	3343	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
1.5 Subgroup analysis: hospitalisation due to respiratory-related illness	5	3343	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
1.5.1 High-income countries	4	3260	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
1.5.2 Low- and middle-income countries	1	83	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.18, 1.22]
1.6 Length of hospital stay	2	2789	Mean Difference (IV, Random, 95% CI)	-42.24 [-84.77, 0.29]
1.7 RSV infection	3	554	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.20, 0.55]
1.8 Number of wheezing days	1	429	Risk Ratio (IV, Random, 95% CI)	0.39 [0.35, 0.44]
1.9 Days of supplemental oxygen	2	2789	Mean Difference (IV, Random, 95% CI)	-36.85 [-85.19, 11.49]
1.10 Intensive care unit length of stay	2	2789	Mean Difference (IV, Random, 95% CI)	-13.51 [-61.11, 34.08]
1.11 Mechanical ventilation days	2	2789	Mean Difference (IV, Random, 95% CI)	5.78 [-10.37, 21.92]

Analysis 1.1. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 1: Hospitalisation due to RSV infection

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Blanken 2013 (1)	2	214	11	215	5.8%	0.18 [0.04 , 0.81]	+	+	+	+	+	+
Feltes 2003 (2)	34	639	63	648	43.9%	0.55 [0.37 , 0.82]	+	+	+	+	+	+
IMpact-RSV Study Group 1998 (2)	48	1002	53	500	47.0%	0.45 [0.31 , 0.66]	+	+	+	+	+	+
Subramanian 1998 (2)	0	22	2	20	1.5%	0.18 [0.01 , 3.59]	+	+	+	+	+	+
Tavsu 2014 (3)	0	41	10	42	1.7%	0.05 [0.00 , 0.81]	?	?	+	+	+	?
Total (95% CI)		**1918**		**1425**	**100.0%**	**0.44 [0.30 , 0.64]**						
Total events:	84		139									



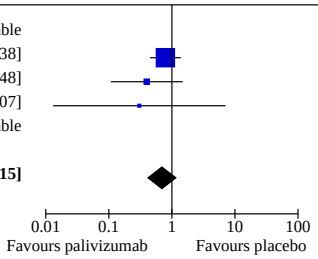
Heterogeneity: Tau² = 0.04; Chi² = 5.18, df = 4 (P = 0.27); I² = 23%
Test for overall effect: Z = 4.29 (P < 0.0001)
Test for subgroup differences: Not applicable

Footnotes
(1) Data from one year follow-up.
(2) 150 days follow-up
(3) Two years follow-up.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 2: Mortality

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Blanken 2013 (1)	0	214	0	215		Not estimable	+	+	+	+	+	+
Feltes 2003 (2)	21	639	27	648	82.4%	0.79 [0.45 , 1.38]	+	+	+	+	+	+
IMpact-RSV Study Group 1998 (3)	4	1002	5	500	15.0%	0.40 [0.11 , 1.48]	+	+	+	+	+	+
Subramanian 1998 (4)	0	22	1	20	2.6%	0.30 [0.01 , 7.07]	+	+	+	+	+	+
Tavsu 2014 (5)	0	41	0	42		Not estimable	?	?	+	+	+	?
Total (95% CI)		**1918**		**1425**	**100.0%**	**0.69 [0.42 , 1.15]**						
Total events:	25		33									



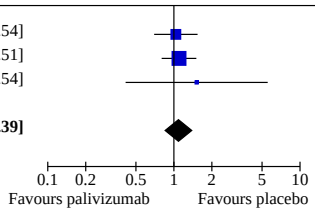
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

Footnotes
(1) The study states that there were no deaths.
(2) The study states that none of the deaths were attributable to palivizumab. Six children in the palivizumab group and five children in the placebo group had surgery-associated deaths. Tw
(3) The study states that none of the deaths were attributable to palivizumab. Two children died in the palivizumab group: one following surgery for tympanostomy tubes after recovery from
(4) One child died in the placebo group due to disseminated adenovirus infection.
(5) The study states that no infants died during follow-up.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 3: Adverse events

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Feltes 2003 (1)	46	639	45	648	37.6%	1.04 [0.70 , 1.54]	+	+	+	+	+	+
IMpact-RSV Study Group 1998 (1)	110	1002	50	500	58.9%	1.10 [0.80 , 1.51]	+	+	+	+	+	+
Subramanian 1998 (1)	5	22	3	20	3.5%	1.52 [0.41 , 5.54]	+	+	+	+	+	+
Total (95% CI)		**1663**		**1168**	**100.0%**	**1.09 [0.85 , 1.39]**						
Total events:	161		98									



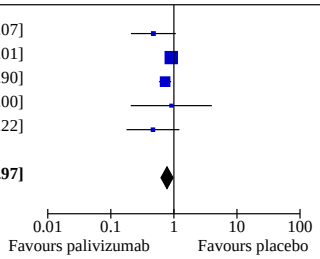
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable

Footnotes
(1) Adverse events that a blinded investigator considered potentially related to the study drug.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 4: Hospitalisation due to respiratory-related illness

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Blanken 2013 (1)	8	214	17	215	6.3%	0.47 [0.21 , 1.07]	+	+	+	+	+	+
Feltes 2003 (2)	321	639	359	648	50.5%	0.91 [0.82 , 1.01]	+	+	+	+	+	+
IMpact-RSV Study Group 1998 (3)	160	1002	110	500	36.4%	0.73 [0.58 , 0.90]	+	+	+	+	+	+
Subramanian 1998 (4)	3	22	3	20	2.1%	0.91 [0.21 , 4.00]	+	+	+	+	+	+
Tavsu 2014 (5)	5	41	11	42	4.7%	0.47 [0.18 , 1.22]	?	?	+	+	+	?
Total (95% CI)		**1918**		**1425**	**100.0%**	**0.78 [0.62 , 0.97]**						
Total events:	497		500									



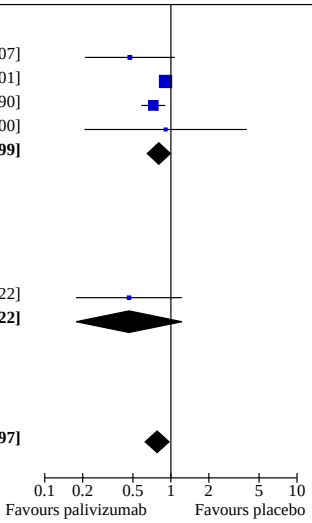
Heterogeneity: Tau² = 0.02; Chi² = 7.32, df = 4 (P = 0.12); I² = 45%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable

Footnotes
(1) Children hospitalised with other respiratory tract illnesses. Data from the one year follow-up.
(2) Children with cardiorespiratory hospitalisation. Data from follow-up at 150 days.
(3) Children with any respiratory-illness related hospitalisation. Data from follow-up at 150 days.
(4) Number of children with any respiratory-illness related hospitalisation. Data from follow-up at 150 days.
(5) Children hospitalised with other respiratory tract illnesses (not RSV). Data from the two years follow-up.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 5: Subgroup analysis: hospitalisation due to respiratory-related illness

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 High-income countries						
Blanken 2013 (1)	8	214	17	215	6.3%	0.47 [0.21 , 1.07]
Feltes 2003 (2)	321	639	359	648	50.5%	0.91 [0.82 , 1.01]
IMpact-RSV Study Group 1998 (3)	160	1002	110	500	36.4%	0.73 [0.58 , 0.90]
Subramanian 1998 (4)	3	22	3	20	2.1%	0.91 [0.21 , 4.00]
Subtotal (95% CI)		**1877**		**1383**	**95.3%**	**0.80 [0.65 , 0.99]**
Total events:	492		489			
Heterogeneity: Tau² = 0.02; Chi² = 5.67, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.5.2 Low- and middle-income countries						
Tavsu 2014 (5)	5	41	11	42	4.7%	0.47 [0.18 , 1.22]
Subtotal (95% CI)		**41**		**42**	**4.7%**	**0.47 [0.18 , 1.22]**
Total events:	5		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		**1918**		**1425**	**100.0%**	**0.78 [0.62 , 0.97]**
Total events:	497		500			
Heterogeneity: Tau² = 0.02; Chi² = 7.32, df = 4 (P = 0.12); I² = 45%						
Test for overall effect: Z = 2.25 (P = 0.02)						
Test for subgroup differences: Chi² = 1.16, df = 1 (P = 0.28), I² = 14.0%						



Footnotes

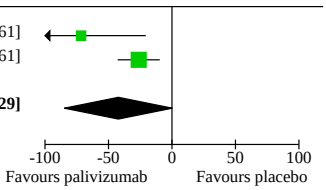
(1) Children hospitalised with other respiratory tract illnesses. Data from the one year follow-up.
(2) Children with cardiorespiratory hospitalisation. Data from follow-up at 150 days.
(3) Children with any respiratory-illness related hospitalisation. Data from follow-up at 150 days.
(4) Number of children with any respiratory-illness related hospitalisation. Data from follow-up at 150 days.
(5) Children hospitalised with other respiratory tract illnesses (not RSV). Data from the two years follow-up.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 6: Length of hospital stay

Study or Subgroup	Palivizumab Mean	Palivizumab SD	Palivizumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Feltes 2003 (1)	57.4	466.61	639	129	466.61	648	35.3%	-71.60 [-122.59 , -20.61]
IMpact-RSV Study Group 1998 (2)	36.4	154.57	1002	62.6	154.57	500	64.7%	-26.20 [-42.79 , -9.61]
Total (95% CI)			**1641**			**1148**	**100.0%**	**-42.24 [-84.77 , 0.29]**
Heterogeneity: Tau² = 656.40; Chi² = 2.75, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 1.95 (P = 0.05)								
Test for subgroup differences: Not applicable								



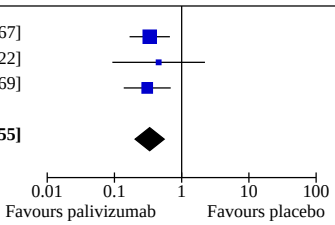
Footnotes

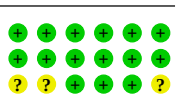
(1) Length of hospital stay during hospitalisation due to RSV infection, measured in total days of hospitalisations per 100 children. SD obtained from P values. The same SD was used for t
(2) Length of hospital stay during hospitalisation due to RSV infection measured in total days of hospitalisations per 100 children. SD obtained from P values. The same SD was used for b

Analysis 1.7. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 7: RSV infection

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Blanken 2013 (1)	10	214	30	215	51.9%	0.33 [0.17 , 0.67]
Subramanian 1998 (2)	2	22	4	20	9.8%	0.45 [0.09 , 2.22]
Tavsu 2014 (3)	6	41	20	42	38.2%	0.31 [0.14 , 0.69]
Total (95% CI)		**277**		**277**	**100.0%**	**0.33 [0.20 , 0.55]**
Total events:	18		54			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 4.32 (P < 0.0001)
Test for subgroup differences: Not applicable





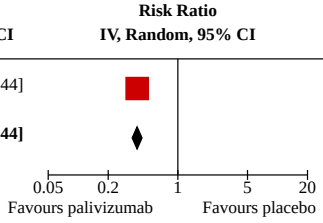
Footnotes
(1) Data from the one year follow-up.
(2) Data from the follow-up after 150 days.
(3) Data from the two years follow-up.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 8: Number of wheezing days

Study or Subgroup	log[RR]	SE	Palivizumab Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Blanken 2013	-0.941609	0.058379	214	215	100.0%	0.39 [0.35 , 0.44]
Total (95% CI)			**214**	**215**	**100.0%**	**0.39 [0.35 , 0.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 16.13 (P < 0.00001)
Test for subgroup differences: Not applicable

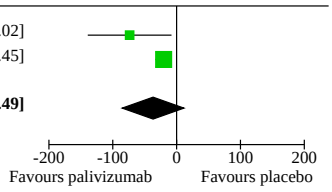


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 9: Days of supplemental oxygen

Study or Subgroup	Palivizumab Mean	Palivizumab SD	Palivizumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Feltes 2003 (1)	27.9	600.13	639	101.5	600.13	648	31.1%	-73.60 [-139.18 , -8.02]
IMpact-RSV Study Group 1998 (1)	30.3	119.76	1002	50.6	119.76	500	68.9%	-20.30 [-33.15 , -7.45]
Total (95% CI)			**1641**			**1148**	**100.0%**	**-36.85 [-85.19 , 11.49]**

Heterogeneity: Tau² = 839.24; Chi² = 2.44, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable

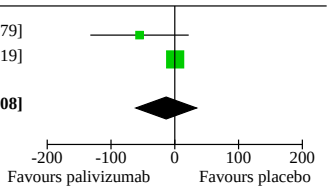


Footnotes
(1) SD obtained from P values. The same SD was used for both Placebo and Palivizumab groups.

Analysis 1.10. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 10: Intensive care unit length of stay

Study or Subgroup	Palivizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Feltes 2003 (1)	15.9	705.54	639	71.2	705.54	648	25.2%	-55.30 [-132.39 , 21.79]
IMpact-RSV Study Group 1998 (1)	13.3	5.49	1002	12.7	5.49	500	74.8%	0.60 [0.01 , 1.19]
Total (95% CI)			**1641**			**1148**	**100.0%**	**-13.51 [-61.11 , 34.08]**

Heterogeneity: Tau² = 788.76; Chi² = 2.02, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

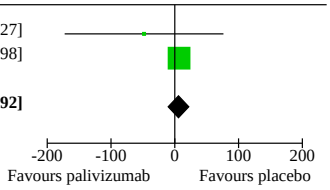


Footnotes
(1) SD obtained from P values. The same SD was used for both Placebo and Palivizumab groups.

Analysis 1.11. Comparison 1: Palivizumab versus placebo or no intervention, Outcome 11: Mechanical ventilation days

Study or Subgroup	Palivizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Feltes 2003 (1)	6.5	1139.1	639	54.7	1139.1	648	1.7%	-48.20 [-172.67 , 76.27]
IMpact-RSV Study Group 1998 (1)	8.4	151.7	1002	1.7	151.7	500	98.3%	6.70 [-9.58 , 22.98]
Total (95% CI)			**1641**			**1148**	**100.0%**	**5.78 [-10.37 , 21.92]**

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Footnotes
(1) SD obtained from P values. The same SD was used for both Placebo and Palivizumab groups.

APPENDICES

Appendix 1. Appendix 1. Search strategies

MEDLINE (Ovid)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 14, 2021

1 Respiratory Syncytial Virus Infections/

2(respiratory syncytial virus* or rsv).tw.

3 respiratory syncytial viruses/ or respiratory syncytial virus, human/

4 exp Bronchiolitis/

5 bronchiolit*.tw.

6 exp Pneumonia/

7 (pneumon* or bronchopneumon* or pleuropneumon*).tw.

8 Respiratory Tract Infections/

9 lower respiratory infection*.tw.

10 (lower respiratory tract infection* or lrti).tw.

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12 Palivizumab/

13 palivizumab.tw,nm.

14 synagis.tw,nm.

15 medi-493.tw,nm.

16 medi493.tw,nm.

17 "medi 493".tw,nm.

18 12 or 13 or 14 or 15 or 16 or 17

19 11 and 18

Embase (Elsevier)

#1. 'respiratory syncytial virus infection'/exp

#2. 'respiratory syncytial virus' OR rsv

#3. 'bronchiolitis'/exp

#4. bronchiolit*:ti,ab,kw

#5. 'pneumonia'/exp

#6. pneumon*:ti,ab,kw OR bronchopneumon*:ti,ab,kw OR pleuropneumon*:ti,ab,kw

#7. 'respiratory tract infection'/exp

#8. 'lower respiratory infection*':ti,ab,kw

#9. 'lower respiratory tract infection*':ti,ab,kw OR lrti:ti,ab,kw

#10. 'pneumovirus'/exp OR 'human respiratory syncytial virus'/exp

#11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12. 'palivizumab'/exp

#13. palivizumab:ti,ab,kw

#14. synagis:ti,ab,kw

#15. 'medi-493':ti,ab,kw

#16. 'medi493':ti,ab,kw

#17. 'medi 493':ab,kw

#18. #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19. #11 AND #18

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Respiratory Syncytial Virus Infections] explode all trees
#2 ((respiratory syncytial virus* or rsv)):ti,ab,kw
#3 MeSH descriptor: [Respiratory Syncytial Viruses] explode all trees
#4 MeSH descriptor: [Respiratory Syncytial Virus, Human] explode all trees
#5 MeSH descriptor: [Bronchiolitis] explode all trees
#6 (bronchiolit*):ti,ab,kw
#7 MeSH descriptor: [Bronchiolitis] explode all trees
#8 ((pneumon* or bronchopneumon* or pleuropneumon*)):ti,ab,kw
#9 MeSH descriptor: [Respiratory Tract Infections] explode all trees

#10 ((lower respiratory infection*)):ti,ab,kw
#11 ((lower respiratory tract infection* or lrti)):ti,ab,kw 3308
#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13 MeSH descriptor: [Palivizumab] explode all trees
#14 ((palivizumab)):ti,ab,kw
#15 (synagis):ti,ab,kw
#16 (medi-493):ti,ab,kw
#17 (medi493):ti,ab,kw
#18 ("medi 493"):ti,ab,kw
#19 #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #12 AND #19

LILACS (BIREME)

(Respiratory Syncytial Virus Infections OR Infecciones por Virus Sincitial Respiratorio OR Infecções por Vírus Respiratório Sincicial OR Bronchiolitis OR bronquiolitis OR Bronquiolite OR Bronchopneumonia OR Bronconeumonía OR Broncopneumonia OR Respiratory Tract Infections OR Infecciones del Sistema Respiratorio OR Infecções Respiratórias) AND (Palivizumab OR Synagis OR MEDI 493 OR MEDI-493 OR MEDI493)

CINAHL

(respiratory syncytial virus infection (rsv) OR Bronchiolitis OR Pneumonia OR Respiratory Tract Infections OR lower respiratory infection) AND (Palivizumab OR synagis OR medi-493 OR Medi 493 OR Medi493)

Scopus

TITLE-ABS-KEY (("respiratory syncytial virus infection" OR bronchiolitis OR pneumonia OR "respiratory tract infections" OR "lower respiratory infection") AND (palivizumab OR synagis OR medi-493 OR medi 493 OR med493))

ClinicalTrials.gov

Intervention: palivizumab OR synagis OR medi-493 OR medi 493 OR med493

WHO ICTRP (Standard search)

palivizumab OR synagis OR medi-493 OR medi 493 OR med493

HISTORY

Protocol first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

LG and JVAF: conceived, designed, and wrote the protocol and full review and performed all aspects of the data abstraction, analysis, risk of bias assessment and certainty of evidence ratings.

IE: drafted the Background section, provided input and literature for the Discussion section and drafted the full review.

LS: performed all aspects of the data abstraction, analysis and risk of bias assessment.

CMEL: designed and ran the electronic searches, and drafted the full review.

PR: reviewed critical content.

All authors read and approved the final draft of the review.

DECLARATIONS OF INTEREST

LG: declared that they have no conflict of interest.
LS: declared that they have no conflict of interest.
PR: declared that they have no conflict of interest.
CMEL: declared that they have no conflict of interest.
IE: declared that they have no conflict of interest.
JVAF: declared that they have no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Instituto Universitario Hospital Italiano, Argentina

  In-kind support for the research team

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the review title to 'Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children' to fit the scope of the review, as suggested by peer reviewers.

We included one trial administrating palivizumab intravenously in order to maximize the use of available information (Subramanian 1998). We highlighted this in the results section.

Change in the outcomes

Mortality: we broadened this definition to "death due to all causes" as it would result in better use of the available information, considering that the trials had not systematically reported this information. Nevertheless, we also reported the cause of deaths for each group (including deaths related to RSV infection) when this information was available.

Length of hospital stay: based on input from the Cochrane Methods Support Unit this outcome was removed from the summary of findings table as it is reported in a subset of patients, which breaks randomisation and is considered a post hoc analysis in the trial that does not include all randomised participants and therefore does not comply with the analyses on the effect of assignment to intervention. We considered it an exploratory outcome and reported it accordingly.

We changed the order of the outcomes in the review. We changed the primary outcome to prevention of RSV hospitalisation and moved hospitalisation due to any respiratory infection to a secondary outcome, as suggested by peer reviewers.

Number of wheezing days: considering that the single included study providing datat for this outcome reported multiple analyses (including the total log days and the total symptoms days), we chose to display the relative reduction in the rate of daily wheezing to avoid any unit of analysis errors.

Search strategy

The search strategy was first performed on 15 October, 2020, and updated in October 2021. However, we did not update the Embase search strategy as we lacked access to the database this year, although the Embase records can be retrieved through CENTRAL.

Methods not implemented

We did not use the search filter for randomised controlled trials (Lefebvre 2019), since we used Screen4Me to identify trials.

Primary outcomes

We intended to report serious adverse events separately, however, the included studies reported the global incidence of adverse events. Nevertheless, we disaggregated some of these events (such as hospitalisation due to respiratory illness and overall mortality).

Subgroup analyses

We were not able to carry out two of our prespecified subgroup analyses (high-risk children versus average-risk children and tropical regions versus non-tropical regions) as we found no studies with these characteristics.
We were able to carry out the remaining subgroup analysis (high-income countries versus low- and middle-income countries) only for the outcome hospitalisation due to respiratory-related illness.

Sensitivity analyses

We moved the specifications regarding sensitivity analysis from the Data synthesis section of the protocol to Sensitivity analysis section in the full review. However, we were unable to carry out any sensitivity analyses due to scarcity of data.

INDEX TERMS

Medical Subject Headings (MeSH)

Hospitalization; Length of Stay; Palivizumab [therapeutic use]; *Respiratory Syncytial Virus Infections [prevention & control]; Respiratory Syncytial Viruses

MeSH check words

Child; Child, Preschool; Humans; Infant; Infant, Newborn