COVID-19 rapid policy statement

# Palivizumab passive immunisation against Respiratory Syncytial Virus (RSV) in at risk pre-term infants

## Introduction

In response to the public health emergency posed by coronavirus disease 2019 (COVID-19), NHS England and NHS Improvement, working with the Devolved Administrations (DAs), has established a rapid policy development process to aid clinicians in offering best care and advice to patients with, or at risk of, COVID-19 across the UK. This document sets out the interim clinical commissioning position for passive immunisation with palivizumab against respiratory syncytial virus (RSV) in at-risk pre-term infants.

## Commissioning position

The proposal is: to extend passive immunisation against RSV with palivizumab in at risk pre-term infants in accordance with the criteria set out in this document.

## Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Plain language summary

In the UK, Respiratory Syncytial Virus (RSV) is a seasonal winter virus causing lower respiratory tract infections (LRTIs) usually from October to March. Most RSV infections occur in a relatively short epidemic of about 6 weeks. LRTI, resulting from RSV, usually causes mild, self-limiting illness, but may cause severe illness in vulnerable infants at high risk of LRTI resulting in hospitalisation.

Palivizumab (administered as an intramuscular injection) is used to provide protection against RSV in at-risk patients, and has been shown to decrease hospitalisation in this group. It is currently part of a UK-wide immunisation schedule as per guidance issued by Joint Committee on Vaccination and Immunisation (JCVI) in 2010, which recommends its use in premature infants with conditions affecting the lungs and/or heart, and children with impaired immune systems.

This policy statement proposes the extension of the eligibility criteria for immunisation with palivizumab (within the context of the current COVID-19 pandemic) to a further group of at-risk infants as set out in this policy. *The proposed extension for palivizumab immunisation is outlined in text on page 4 and pictorially as an algorithm in Appendix 1.*

## Overview

### The condition

RSV infection manifests predominantly as a respiratory illness and is responsible for 75-80% of all LRTI cases in young children (Green CA, 2016). It is one of the leading causes of hospitalisation in the first year of life. Previous infection with RSV may only confer partial immunity and so individuals may be repeatedly infected with the same or different strains of RSV.

In most cases, the infection is mild and self-limiting but severe illness may occur in vulnerable infants, resulting in hospitalisation and/or admission to intensive care. Babies at highest risk of serious RSV illness are pre-term infants with conditions that predispose them to complications from RSV infection such as chronic lung disease (CLD – also known as bronchopulmonary dysplasia [BPD]), congenital heart disease (CHD), multiple congenital anomalies and immunodeficiencies.

### Intervention

Palivizumab is a recombinant humanised monoclonal antibody directed against the F-protein on the surface of the RSV. It is a form of passive immunisation, not a vaccine, and as such only provides short-term protection against RSV. Up to five intramuscular doses (of 15mg/kg) at monthly intervals are usually administered over the RSV season[1]. Commonly occurring adverse events or side effects include injection site reactions, fever, and diarrhoea.

### Current Treatment

The JCVI guidance in the UK currently recommends the use of palivizumab prophylaxis to protect at-risk infants in whom RSV infection is likely to cause serious illness or death (JCVI, 2010). Palivizumab prophylaxis in the UK is currently recommended for use in children in the age groups displayed in Table 1 AND meeting any of the clinical criteria below the table (the relevance of the shaded areas is explained further in the text below the table):

[1] Usually defined as the beginning of calendar week 40 (i.e. the beginning of October) to the end of calendar week 8 (i.e. the end of February) the following year

| | Gestational age at birth (weeks) | | | | | |
|---|---|---|---|---|---|---|
| **Chronological age (months)** | **≤24$^{+0}$** | **24$^{+1}$ to 26$^{+0}$** | **26$^{+1}$ to 28$^{+0}$** | **28$^{+1}$ to 30$^{+0}$** | **30$^{+1}$ to 32$^{+0}$** | **32$^{+1}$ to 34$^{+0}$** |
| <1.5 | | | | | | |
| 1.5 to <3 | | | | | | |
| 3 to <6 | | | | | | |
| 6 to <9 | | | | | | |

***Table 1: Cost-effective use of palivizumab. Reproduced from the JCVI statement on RSV immunisation, 2010***

- Represents age cohorts for which palivizumab would be cost-effective in the presence of CLD only
- Represents age cohorts for which palivizumab would be cost-effective in the presence of CLD and CHD

1. **High risk due to BPD – also known as CLD**
   a) Pre-term infants who have moderate or severe BPD[2]. Pre-term infants who have BPD and meet the gestational age and chronological age criteria at the start of the RSV season in **all** the shaded areas of Table 1 above qualify for treatment.
   b) Infants with respiratory diseases who are not necessarily pre-term but who remain on oxygen at the start of the RSV season are also considered to be at higher risk. These may include:
      - Pulmonary hypoplasia due to congenital diaphragmatic hernia
      - Other congenital lung abnormalities[3]
      - Interstitial lung disease

      **and** including those receiving long-term ventilation at the onset of the RSV season[4].
2. **High risk due to CHD**
   a) Pre-term infants with haemodynamically significant, acyanotic CHD who meet the gestational age and chronological age criteria in the **dark grey** shaded areas in Table 1 at the start of the RSV season.
   b) Cyanotic or acyanotic CHD plus significant co-morbidities.
3. **Children less than 24 months of age with severe combined immunodeficiency disease (SCID).** This is the most severe form of inherited deficiency of immunity, in which children are unable to mount either T-cell responses or produce antibody against infectious agents**.**

These criteria are more restrictive than in other developed countries where the immunisation is given to a wider population of children (Luna MS, 2020). Palivizumab is currently the only licensed intervention for the prevention of RSV infection and there are no alternative interventions at present.

[2] Moderate or severe BPD is defined as pre-term infants with compatible x-ray changes who continue to receive supplemental oxygen or respiratory support at 36 weeks post-menstrual age
[3] Sometimes also involving congenital heart disease or lung malformation
[4] Any child who when medically stable, continues to require a mechanical aid for breathing, after an acknowledged failure to wean three months after the institution of ventilation (Jardine and Wallis, 1998) is defined as receiving long-term ventilation.

### Proposed Treatment

In light of the present COVID-19 pandemic, it has been proposed that these criteria be widened to include a larger population of at-risk infants to decrease hospitalisation and intensive care admission rates with the aim of reducing the risk of nosocomial infection and pressure on the health system. This would include at-risk pre-term infants[5] with CLD or BPD in their first year of life (Sommer C, 2014).

## Evidence summary

An evidence review of three academic publications on the use of palivizumab immunisation against RSV in at-risk infants was conducted by Solutions for Public Health (SPH). The evidence of effectiveness of palivizumab in infants with co-morbidities is well recognised. The evidence review by SPH suggested some benefit with palivizumab passive immunisation in preventing RSV hospital admissions in infants born pre-term with and without co-morbidities such as BPD. The summary of the evidence from the three papers is in Appendix 2.

## Implementation (extended use of palivizumab)

### Eligibility criteria

Infants who meet the current JCVI recommendations will continue to be eligible for palivizumab. *In addition*, during the COVID-19 pandemic, the following additional access criteria are permitted:

- Infants born at ≤$34^{+0}$ weeks gestation; **AND**
- Diagnosed with CLD[6]; **AND**
- Discharged from hospital on home oxygen in the 9 months prior to the start of the RSV season (for the start of the 2021/2022 RSV season this is for patients discharged on or after 1 October 2020).

### Dose

The recommended dose of palivizumab is 15mg/kg of body weight, given once a month. Where possible the first dose should be administered at the start of the RSV season. **Subsequent doses should be administered monthly throughout the RSV season for up to a maximum of seven doses.** Where the course of treatment begins later in the RSV season then up to seven doses should be given one month apart until the end of the RSV season.

### Contraindications and precautions

Palivizumab should **not** be given to infants or children who have had:

- A confirmed anaphylactic reaction to a previous dose of palivizumab
- A confirmed anaphylactic reaction to any components of palivizumab

[5] Defined as being born at ≤34 weeks gestational age

[6] Defined for the purpose of this policy as “preterm infants with compatible x-ray changes who continue to receive supplemental oxygen or respiratory support at 36 weeks post-menstrual age” (Department of Health, 2015). Please note that the JCVI define CLD as “oxygen dependency for at least 28 days from birth” (JCVI, 2010).

- A confirmed anaphylactic reaction to another humanised monoclonal antibody.

Palivizumab should be given with caution to patients with thrombocytopenia or any coagulation disorder.

A mild febrile illness, such as mild upper respiratory tract infection, is not usually reason to defer administration of palivizumab. A moderate to severe acute infection or febrile illness may warrant delaying the use of palivizumab unless, in the opinion of the physician, withholding palivizumab entails a greater risk.

### Safety reporting

Any suspected adverse drug reactions (ADRs) for patients receiving palivizumab should be reported directly to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme at https://yellowcard.mhra.gov.uk/.

## Governance

### Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

### Effective from

This policy will be in effect from the date of publication.

### Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy pertains to the COVID-19 pandemic and the RSV season (2020/21) and will be reviewed periodically.

## Definitions

| | |
|---|---|
| **Bronchopulmonary dysplasia (BPD)** | A form of lung disease found in infants that were born prematurely due to incomplete development of the lungs and airways. Its defining criterion is the requirement for respiratory support at 36 weeks gestational age. |
| **Chronic lung disease (CLD)** | Also known as chronic lung disease of prematurity or chronic neonatal lung disease and is used interchangeably with BPD. |
| **Respiratory Syncytial Virus (RSV)** | An enveloped RNA pneumovirus that is a common cause of respiratory tract infection. |

## References

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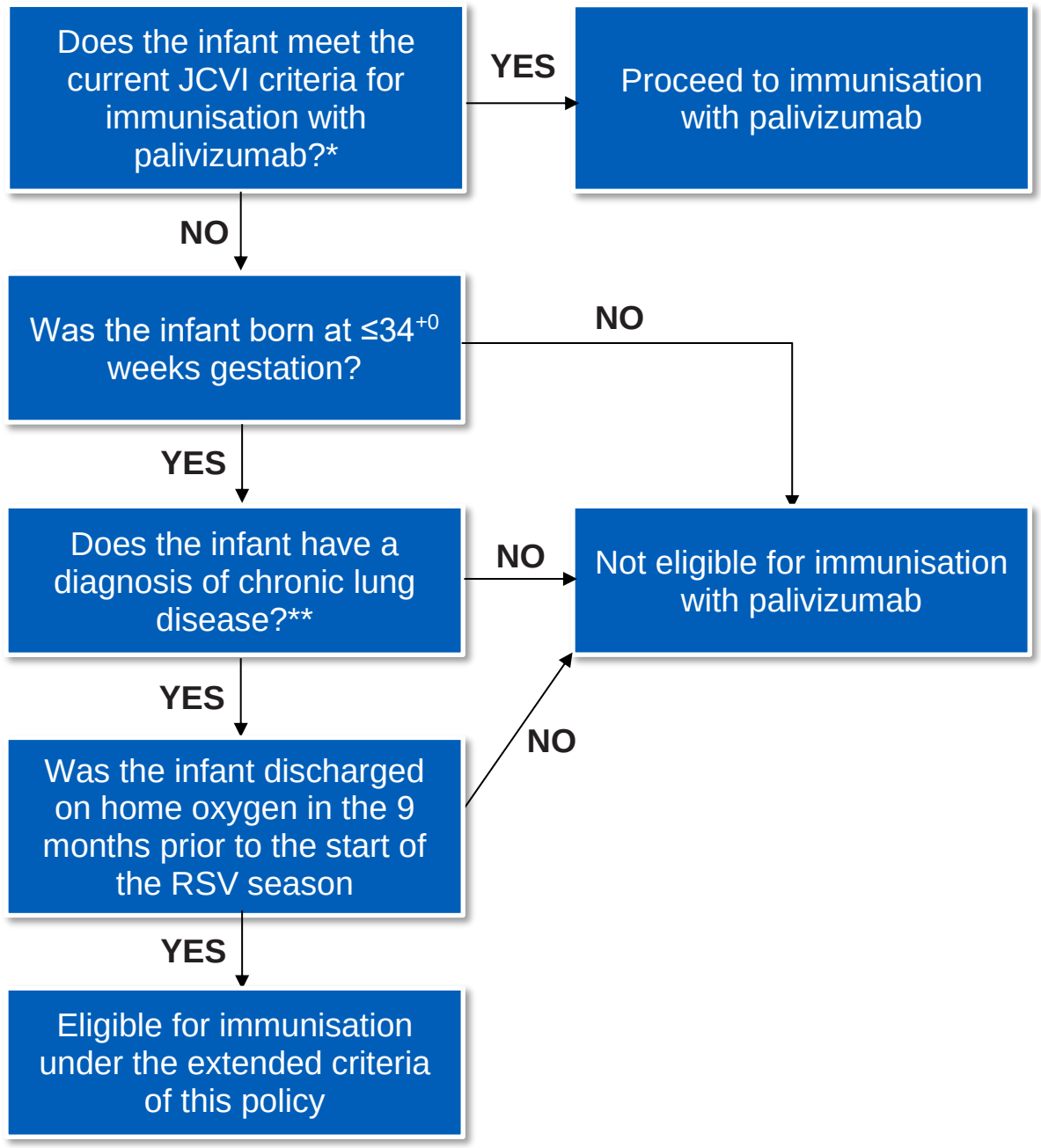
## Appendix 1

**Algorithm for immunisation with palivizumab under the extended access criteria**




* See p2-3 of this document for current JCVI criteria
** Defined for the purpose of this policy as “preterm infants with compatible x-ray changes who continue to receive supplemental oxygen or respiratory support at 36 weeks post-menstrual age” (Department of Health, 2015). Please note that the JCVI define CLD as “oxygen dependency for at least 28 days from birth” (JCVI, 2010).

## Appendix 2: Extending palivizumab immunisation for respiratory syncytial virus (RSV) in at risk groups of infants to prevent hospitalisation during the winter season

### Narrative summary of papers presented for review

Three papers were presented for review by NHS England.

- Paper 1, the IMpact-RSV trial, is a randomised controlled trial conducted in 139 centres in the US, UK and Canada including 1,502 children of whom 740 were premature but did not have bronchopulmonary dysplasia (BPD).
- Paper 2 is a prospective single-arm multicentre study in 18 hospitals in Canada, evaluating 444 children who received palivizumab of whom 324 were premature and did not have BPD.
- Paper 3 is a prospective observational study in 12 hospitals in Burgundy, France, evaluating palivizumab for premature infants without BPD in two RSV seasons compared to three previous seasons when it was not used.

#### Paper 1: IMpact-RSV Study Group 1998. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants

This paper reports a randomised double-blind placebo-controlled trial conducted in 119 centres in the US, 11 in the UK and nine in Canada during the 1996 to 1997 RSV season. The study included children who were either ≤35 weeks gestation and ≤6 months old or were ≤24 months old with a diagnosis of BPD requiring ongoing treatment. Exclusion criteria included hospitalisation at entry anticipated to last >30 days, mechanical ventilation at entry, life expectancy <6 months, active or recent RSV infection, hepatic or renal dysfunction, seizure disorder, a group of congenital heart diseases, immunodeficiency, and relevant allergy or previous related treatment.

A total of 1,502 children were randomised, 500 to placebo and 1,002 to palivizumab prophylaxis, of whom 123 (8%) were in the UK. 740 (234 in the placebo and 506 in the palivizumab group) were ≤35 weeks gestation, up to six months old and did not have BPD. 762 (266 in the placebo and 496 in the palivizumab group) were up to 24 months old with a diagnosis of BPD requiring ongoing treatment.

For the whole trial population (not reported separately for the subgroups that did and did not have BPD), 56.9% and 56.8% were male in the palivizumab and placebo groups respectively, mean birth weight was 1.3kg in both groups and mean gestational age was 29 weeks in both groups. 63.0% of the palivizumab group and 68.6% of the placebo group had no smoker in the household (p=0.039, the only significant difference reported in baseline characteristics). Treatment was with 15mg/kg palivizumab or an identically appearing placebo by intramuscular injection every 30 days for five doses.

Follow-up was for 150 days from randomisation (including at each visit, each hospital day[7] and 30 days after the last scheduled injection). Of the whole study population, 99% completed follow-up; 94% of placebo and 92% of the palivizumab group received all five injections; more than 95% in both groups received at least four injections; the proportions receiving none, one, two and three injections were similar in both groups. These data were not reported separately for the groups that did and did not have BPD.

**Paper 2: Oh et al 2002. Palivizumab prophylaxis for respiratory syncytial virus in Canada: utilization and outcomes**

This paper reports a prospective single-arm multicentre study in 18 sites in six provinces of Canada that aimed to provide insight into the use of palivizumab in practice. Children were eligible if they 1) were enrolled through the 1999/2000 Canadian Therapeutic Products Programmes' Special Access Programme, born at ≤32 weeks gestation and <6 months of age at the onset of the RSV season or 2) were <2 years old at the onset of the RSV season and had required oxygen therapy in the six months preceding the RSV season or 3) had a palivizumab request approved for another reason. Children were excluded if receiving palivizumab through a clinical trial or the parent/caregiver was unable to read or write English or French.

A total of 480 children were enrolled: 59.6% were male; mean gestational age was 29.4 weeks; mean birth weight 1383 grams; and 22.6% had smoking in the home. 345 of the children were ≤32 weeks gestation and did not have BPD. For this group, 58.0% were male; mean gestational age was 29.4 weeks; mean birth weight was 1368 grams; and 24.6% had smoking in the home. The 444 children for whom data were available received a total of 1,702 injections of palivizumab over an 8 month period, with 158, 28 and 3 children receiving five, six and seven injections respectively; those who started prophylaxis earlier in the RSV season tended to receive a greater number of injections; the mean number of injections was 3.83; 77% of doses were given 30 +/-5 days after the previous injection; 11.5% experienced an interruption in dosing schedule; the mean dose was 77mg (data not reported for the subgroups separately).

Follow-up was with the parent or caregiver by telephone on a monthly basis until the end of the RSV season followed by contact with the physician (for outpatients) or review of hospital records (for inpatients) if the caregiver reported a respiratory infection. 36 (7.5%) of the original group of 480 were lost to follow-up. Of the remaining 444 children, 12 discontinued palivizumab, due to: parental decision (5); lack of efficacy (3); perceived side effects (2); death from unrelated cause (2).

**Paper 3: Grimaldi et al 2007. Palivizumab efficacy in preterm infants with gestational age ≤30 weeks without BPD**

This paper reports a prospective observational study in Burgundy, France, which included all children ≤30 weeks gestation without BDP cared for in a single regional neonatal intensive care unit during the 1999 to 2004 RSV seasons. Palivizumab prophylaxis (15mg/kg) was administered on discharge from hospital for infants of ≤30 weeks gestation without BPD (defined as oxygen dependence on day 28 of extra-uterine life) in the 2002 to 2003 and 2003 to 2004 RSV seasons where birth date was between 15th April and 31st January and the child was <6 months old at the start of the RSV season. In the previous three RSV seasons (1999 to 2002), children ≤30 weeks gestation without BPD did not receive palivizumab.

[7] It was not clear, but this is likely to refer to each monthly visit for a palivizumab injection and each day in hospital if admitted.

In the three RSV seasons prior to use of palivizumab, there were 118 children ≤30 weeks gestation without BPD. In the following two RSV seasons where palivizumab was available to this group, there were 88 children ≤30 weeks gestation without BPD, of whom 70 (79.5%) received palivizumab. For the other 18 children: parents refused palivizumab (1 child); it was inadvertently missed (4 children); baby was born in late January and discharged after 1st April (lower risk of RSV exposure, 13 children). The mean gestational age was similar across the five RSV seasons between 1999 and 2004, ranging from 28.2 to 28.5 weeks. The mean birth weight in the same five RSV seasons ranged from 1,126 to 1,163 grams.

## Effectiveness

### Incidence of RSV hospitalisation

In the IMpact-RSV trial 1998, children with respiratory hospitalisations were tested for RSV. The authors reported that, for the whole trial population, 48[8] of 1002 (4.8%) in the palivizumab group were hospitalised for RSV compared to 53 of the 500 (10.6%) in the placebo group, a reduction of 55% (95% confidence interval (CI) 38 to 72, p=0.00004). Among the 123 children in the UK, 3 of 83 children (3.6%) in the palivizumab group and 4 of 40 (10%) in the placebo group had respiratory hospitalisations for RSV, a reduction of 64% with palivizumab.

There was a significant reduction in RSV hospitalisations for those <32 weeks gestation (47%, p=0.003); for those of 32 to 35 weeks gestation (80%, p=0.002); for those weighing >5kg (51%, p=0.014); and for those weighing ≤5kg (57%, p=0.001). After adjusting for gender, entry age, entry weight, and BPD in a logistic regression model, gestational age was not a significant predictor of RSV hospitalisation and the palivizumab effect remained statistically significant (p<0.001).

The IMpact-RSV trial 1998 reported that, for the 740 children ≤35 weeks gestation without BPD, 9 of 506 (1.8%) were hospitalised for RSV in the palivizumab group compared to 19 of 234 (8.1%) in the placebo group, a reduction of 78% (95% CI 66 to 90, p<0.001).

The IMpact-RSV trial 1998 reported that, for the 762 children with a diagnosis of BPD requiring ongoing treatment, 39 of 496 (7.9%) were hospitalised for RSV in the palivizumab group compared to 34 of 266 (12.8%) in the placebo group, a reduction of 39% (95% CI 20 to 58, p=0.038).

Oh et al 2002 reported that, of the whole trial population (data available for 444 of 480 children), 27 children were hospitalised for respiratory tract infections (RTIs). Among these, 25 had a total of 28 admissions for lower RTIs (LRTIs), of which nine were RSV-positive and 12 were RSV negative (not all were tested for RSV). The incidence of RSV-positive LRTIs requiring hospitalisation was 2.4%.[9] Compared with children who were not hospitalised for RSV-positive LRTIs (n=435), children hospitalised for RSV-positive LRTIs (n=9) were significantly more likely to have BPD (55.6% vs 20.7%, p=0.03), and more likely (non-significant differences) to have siblings (66.6% vs 46.6%, p=0.14), to be non-Caucasian (33.3% vs 15.1%, p=0.14), to have received mechanical ventilation as a neonate (88.9% vs 67.6%, p=0.18) and to reside in smoking households (44.4% vs 21.7%, p=0.19). Two children were hospitalised for RTIs more than once, all their five hospitalisations being in April or May after their last injection.

[8] It is not clear whether any children were hospitalised more than once for RSV. The wording suggests that the numbers reported refer to number of children hospitalised rather than total number of hospitalisations.
[9] It is not clear from the numbers reported how this and other percentages were calculated by Oh et al 2002.

Oh et al 2002 reported that, among premature (≤32 weeks gestation) children without BPD (data available for 324 of 345 children), nine children[10] were hospitalised for RTIs. Among these nine, eight had LRTIs of which four were RSV-positive and two were RSV negative. The incidence of RSV-positive LRTIs requiring hospitalisation in this group was 1.6%.

Oh et al 2002 reported that, among the children with BPD (data available for 35 of 40 children), eight were hospitalised for RTIs. All eight had LRTIs of which one was RSV-positive and six were RSV negative. The incidence of RSV-positive LRTIs requiring hospitalisation in this group was 3.3%.

Oh et al 2002 reported that, among the premature (≤32 weeks gestation) children who also had BPD (data available for 60 of 68 children), nine were hospitalised for RTIs. Among these nine, eight had LRTIs of which four were RSV-positive and three were RSV negative. The incidence of RSV-positive LRTIs requiring hospitalisation in this group was 7.6%.

Oh et al 2002 reported that, among the children who received palivizumab for another reason (data available for 25 of 27 children), one was hospitalised for a RTI, which was a RSV-negative LRTI; the incidence of RSV-positive LRTIs in this group was 0%.

Grimaldi et al 2007 obtained data for all children in their study cohort who were hospitalised with RSV bronchiolitis[11] at any of the 12 hospitals in the Burgundy region which accepted children during the five RSV seasons from 1st December to 30th April between 1999 and 2004. All children hospitalised for bronchiolitis were screened for RSV.

The authors reported that for children ≤30 weeks gestation without BPD (their study cohort), the RSV bronchiolitis hospitalisation rate was significantly lower in the two seasons with palivizumab prophylaxis compared to the previous three seasons where it was not administered: 1.1% vs 13.5%, p<0.0001 (1 RSV hospitalisation among 88 children of whom 70 received palivizumab vs 16 among 118 children in the years preceding palivizumab use).[12] The child with an RSV bronchiolitis hospitalisation in the palivizumab group had received three palivizumab treatments prior to hospitalisation. The number needed to treat in order to prevent one RSV bronchiolitis hospitalisation was 6 (95% CI 4 to 11).

**Total days of RSV hospitalisation**

The IMpact-RSV trial 1998 reported, for the whole trial population, significantly fewer days (per 100 children) of RSV hospitalisation in the palivizumab group (36.4 days for the palivizumab group vs 62.6 days for the placebo group, p<0.001). Seven in the palivizumab group (0.7%) and three in the placebo group (0.6%) had RSV hospitalisations of 14 days or longer.

**Days of RSV hospitalisation with increased supplemental oxygen requirement**

The IMpact-RSV trial 1998 reported, for the whole trial population, significantly fewer days (per 100 children) of RSV hospitalisation with increased supplemental oxygen requirement in the palivizumab group compared to the placebo group (30.3 vs 50.6 days, p<0.001).

**Days of RSV hospitalisation with a moderate or severe lower respiratory tract illness/infection (LRI)**

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[11] Bronchiolitis was defined as an acute LRTI occurring during an epidemic season in infants presenting with wheezing, retractions, and/or tachypnoea. Criteria for hospitalisation were not predefined.

[12] In the 1999 to 2000, 2000 to 2001 and 2001 to 2002 RSV seasons where palivizumab was not administered, there were 3 RSV hospitalisations in 21 children (14.3%), 8 in 48 (16.7%) and 5 in 49 (10.2%) respectively. Corresponding figures for the 2002 to 2003 and 2003 to 2004 RSV seasons where palivizumab was administered to 29 and 41 children respectively were 0 in 38 (0%) and 1 in 50 (2.0%) RSV hospitalisations respectively.

The IMpact-RSV trial 1998 reported, for the whole trial population, significantly fewer days (per 100 children) of RSV hospitalisation with an LRI score[13] of 3 or greater in the palivizumab group compared to the placebo group (29.6 vs 47.4 days, p<0.001).

**ICU admission during RSV hospitalisation**

The IMpact-RSV trial 1998 reported, for the whole trial population, a significantly smaller proportion requiring ICU admission during RSV hospitalisations: 1.3% of palivizumab recipients[14] compared to 3% of placebo patients (p=0.026). Total days spent in ICU were also significantly fewer: 13.3 compared to 12.7 respectively (p=0.023).[15]

**Mechanical ventilation during RSV hospitalisation**

The IMpact-RSV trial 1998 reported, for the whole trial population, no significant differences in incidence of mechanical ventilation during RSV hospitalisation (0.7% for palivizumab recipients vs 0.2% for the placebo group, p=0.280) or total days of mechanical ventilation (8.4 days vs 1.7 days respectively, p=0.210).[16]

**Clinical events or hospitalisation for any reason**

Oh et al 2002 reported that, for the whole trial population (444 evaluable subjects), there were 148 clinical events or hospitalisations including 116 RTIs (in 91 children, 71 of whom had only one RTI), 25 respiratory events deemed unlikely to be RSV-related by the physician and seven non-respiratory events.

**Hospitalisation for any reason**

The IMpact-RSV trial reported, for the whole trial population, significant differences in incidence of all hospitalisations (24% for palivizumab recipients vs 31% for the placebo group, p=0.011) and total days in hospital per 100 children (191 vs 242 days respectively, p=0.005).

**Respiratory hospitalisation**

The IMpact-RSV trial 1998 reported, for the whole trial population, significant differences in incidence of all respiratory hospitalisation (16% for palivizumab recipients vs 22% for the placebo group, p=0.008) and total days of respiratory hospitalisation per 100 children (124 vs 180 days respectively, p=0.004).

**Respiratory hospitalisation unrelated to RSV**

The IMpact-RSV trial 1998 reported, for the whole trial population, no significant differences in incidence of respiratory hospitalisations unrelated to RSV (13% for palivizumab recipients vs 14% for the placebo group, p=0.470) and total days per 100 children (88 vs 118 days respectively, p=0.369).

Oh et al 2002 reported that, for the trial as a whole (444 evaluable subjects), there were ten hospitalisations for respiratory events that were deemed unlikely to be RSV-related RTIs by the treating physician (three were tested for RSV and were negative).

**Respiratory events managed as outpatients**

[13] Lower Respiratory Tract Illness/Infection (LRI) Score: 0 = no respiratory illness/infection; 1 = upper respiratory tract illness/infection; 2 = mild LRI; 3 = moderate LRI; 4 = severe LRI; 5 = mechanical ventilation.
[14] The words “palivizumab recipients” is used instead of “the palivizumab group” by the authors for these outcomes. It suggests that those who did not receive palivizumab are not included in the denominator for these outcomes.
[15] Patient numbers were not reported for this outcome; the significance test would have taken into account the different number of children in the palivizumab and placebo groups.
[16] Patient numbers were not reported for this outcome.

Oh et al 2002 reported that, for the whole trial population (444 evaluable subjects), there were 99 respiratory events that were managed as outpatients (70 patients, 57 with a single event). 86 of these respiratory events were confirmed RTIs, the majority being managed in either the physician's office (43%) or the emergency room (36%). These included 26 LRTIs (24 patients, five tested for RSV and all five were positive) and 60 upper RTIs (49 patients). For the other 13 respiratory events, the physician indicated to the parent/caregiver that they were unlikely to be RSV related.

### Otitis media

The IMpact-RSV trial 1998 reported, for the whole trial population, no significant difference in the proportion of children with at least one episode of otitis media (42% in palivizumab recipients vs 40% in the placebo group, p=0.505).

## Safety

### Adverse events related to the treatment

The IMpact-RSV trial 1998 reported adverse events for the whole trial group only (n=1,502) and not separately for those who were premature and did or did not have BPD. They reported adverse events judged by the blinded investigator to be related to the study treatment for 11% of the palivizumab group and 10% of the placebo group. No statistically significant differences were reported in relation to events by body system (Table 2).

Discontinuation of injections because of adverse events was rare (0.3%). 2.7% of the palivizumab group and 1.8% of the placebo group reported adverse events related to the injection site[17] including erythema (1.4% vs 1.2%), pain (0.6% vs 0.0%), induration/swelling (0.6% vs 0.2%), and bruising (0.3% vs 0.4%). These were generally mild and of short duration; none were serious.

There were mild or moderate elevations of aspartate aminotransferase (AST) in 3.6% of the palivizumab group and 1.6% of the placebo group, with corresponding figures for alanine aminotransferase (ALT) being 2.3% and 2.0%.[11] Elevations of creatinine, blood urea nitrogen and renal adverse events were infrequent and at a similar rate in both groups.

[17] These figures are taken from the narrative in the paper and differ from those reported in Table 3 in the paper. Table 3 reported lower percentages with an injection site reaction and with elevated AST or ALT than reported in the narrative. The reason for this was not clear.

**Table 2: Most frequently reported adverse events that were judged by the blinded investigator as potentially related to the study drug (IMpact-RSV trial 1998)**

| | Palivizumab | Placebo | p value |
|---|---|---|---|
| Fever | 2.8% | 3.0% | 0.870 |
| Nervousness | 2.5% | 2.6% | 0.865 |
| Injection site reaction[18] | 2.3% | 1.6% | 0.444 |
| Diarrhoea | 1.0% | 0.4% | 0.357 |
| Rash | 0.9% | 0.2% | 0.179 |
| Upper respiratory tract illness | 0.3% | 0.4% | 1.000 |
| Aspartate aminotransferase (AST) increased[12] | 0.5% | 0.6% | 0.726 |
| Alanine aminotransferase (ALT) increased[12] | 0.3% | 0.4% | 0.670 |
| Liver function abnormal (primarily elevations of both AST and ALT) | 0.3% | 0.2% | 1.000 |
| Vomiting | 0.3% | 0.4% | 0.670 |
| Cough | 0.3% | 0.2% | 1.000 |

Oh et al 2002 reported that palivizumab was discontinued for two children because of perceived side effects based on parent or caregiver reports. No further details were provided.

Grimaldi et al 2007 did not specifically report adverse events. However, among the reasons reported for why some in the palivizumab group were not given palivizumab, none were reported to have had it discontinued because of side effects related to previous doses.

**Deaths**

The IMpact-RSV trial 1998 reported four deaths (0.4%) in the palivizumab group and five deaths (1.0%) in the placebo group during the trial, two and zero respectively occurred during hospitalisation for RSV, but no death was judged to be related to palivizumab.

**Immunogenicity**

The IMpact-RSV trial 1998 measured anti-palivizumab binding at intervals during the study. Titres greater that 1:40 were found in 1.2% of the palivizumab group and 2.8% of the placebo group, but they were generally single elevations and not associated with a pattern of adverse events or low palivizumab concentrations.

[18] These results are taken from Table 3 in the paper and differ from those reported in the narrative. Table 3 reported lower percentages with an injection site reaction and with elevated AST or ALT than reported in the narrative. The reason for this was not clear.

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