# Joint Committee on Vaccination and Immunisation Statement on immunisation for Respiratory Syncytial Virus

## Introduction

1. This statement summarises a recommendation from the Joint Committee on Vaccination and Immunisation (JCVI) on an immunisation to prevent serious Respiratory Syncytial Virus (RSV) disease in at risk pre-term infants. It follows a request from the Department of Health that the JCVI consider cost-effective immunisation strategies to protect against RSV[a].

## Background

2. RSV is a common cause of respiratory tract infection. It usually causes a mild self-limiting respiratory infection in adults and children and is an established cause of bronchiolitis in infants. RSV infection can be severe in infants who are at increased risk of acute lower respiratory tract infection (LRTI) and may lead to hospitalisation and in some cases to admission to intensive care. Those most at risk are infants born prematurely who also have conditions that predispose them to complications from RSV infection such as Chronic Lung Disease (CLD), Congenital Heart Disease (CHD) and / or a weakened immune system. RSV infection is a significant burden on health globally; it is a leading cause of childhood hospital admission and a cause of death from LRTI[1]. RSV may be associated with short and, potentially long-term, complications that include breathing difficulties and cardiovascular abnormalities[2]. Previous infection with RSV may only confer partial immunity to RSV and so individuals may be repeatedly infected with the same or different strains of RSV[3].

3. RSV infection is seasonal, occurring in the UK within the period from October to March each year with most infections occurring in a relatively short epidemic of about six weeks (Health Protection Agency, Figure 1a)[4]. Most confirmed diagnoses of RSV infection are in children aged less than one year, followed by those aged between one and four years (Figure 1b)[5].

4. An antibody directed against a surface protein of RSV has been developed, called Palivizumab[6,7]. It is a passive immunisation, not a vaccine, and as such only provides short-term protection against RSV. It has been shown to be safe and effective in reducing RSV hospitalisation rates and serious complications among high-risk children[8,9]. Palivizumab, marketed by Abbott Laboratories Ltd as Synagis® is the only licensed immunisation available for children at high-risk from RSV disease[10,11]. There is no licensed vaccine for RSV.

## JCVI consideration

5. The JCVI RSV sub-committee met on three occasions during 2009 and 2010 to formulate advice on the use of Palivizumab[b]. The evidence that was considered is listed at Appendix A, which included two Health Technology Assessments (HTA) that formed the basis of much of the sub-committee's advice. JCVI reviewed and endorsed the final advice from the sub-committee[c].

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[a] Letter from Secretary of State for Health to JCVI (2009)

[b] JCVI RSV sub-committee minutes : 27 March 2009; 11 December 2009; 8 June 2010

[c] JCVI minutes: 17 June 2009; 14 October 2009; 3 February 2010; 16 June 2010

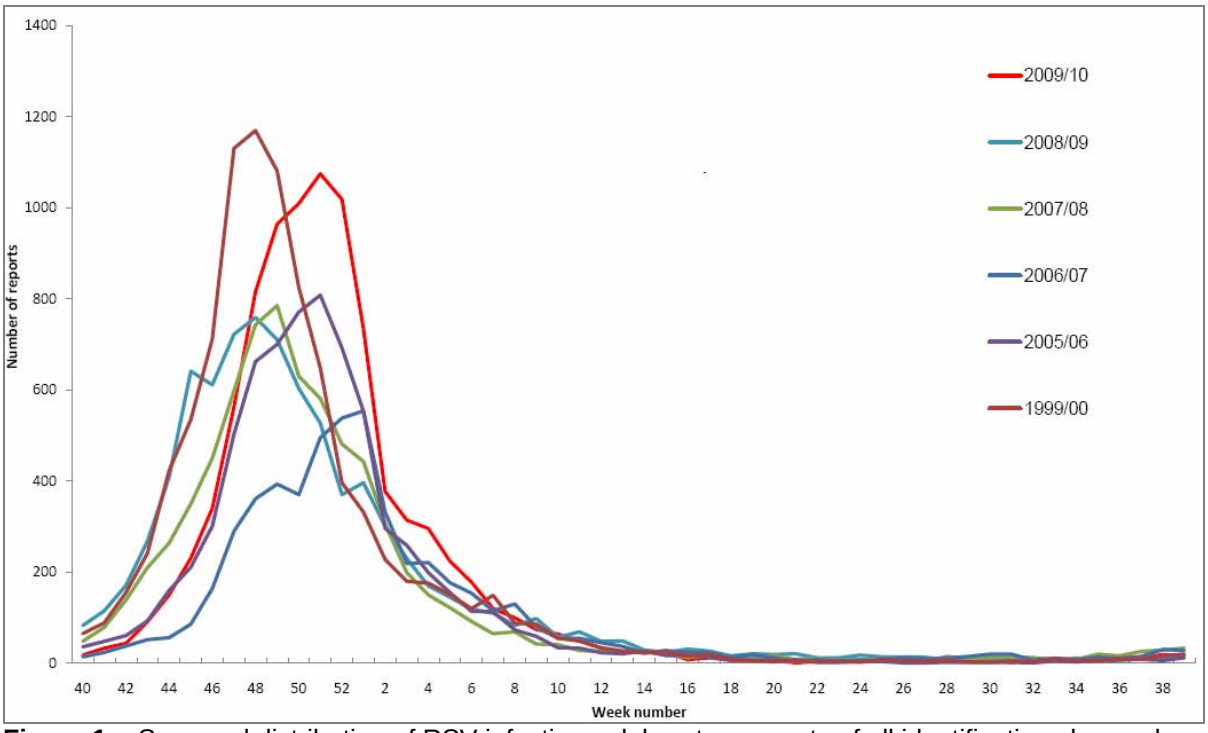


**Figure 1a:** Seasonal distribution of RSV infections - laboratory reports of all identifications by week, England & Wales 1999 – 2010 [Source: Health Protection Agency[4]].

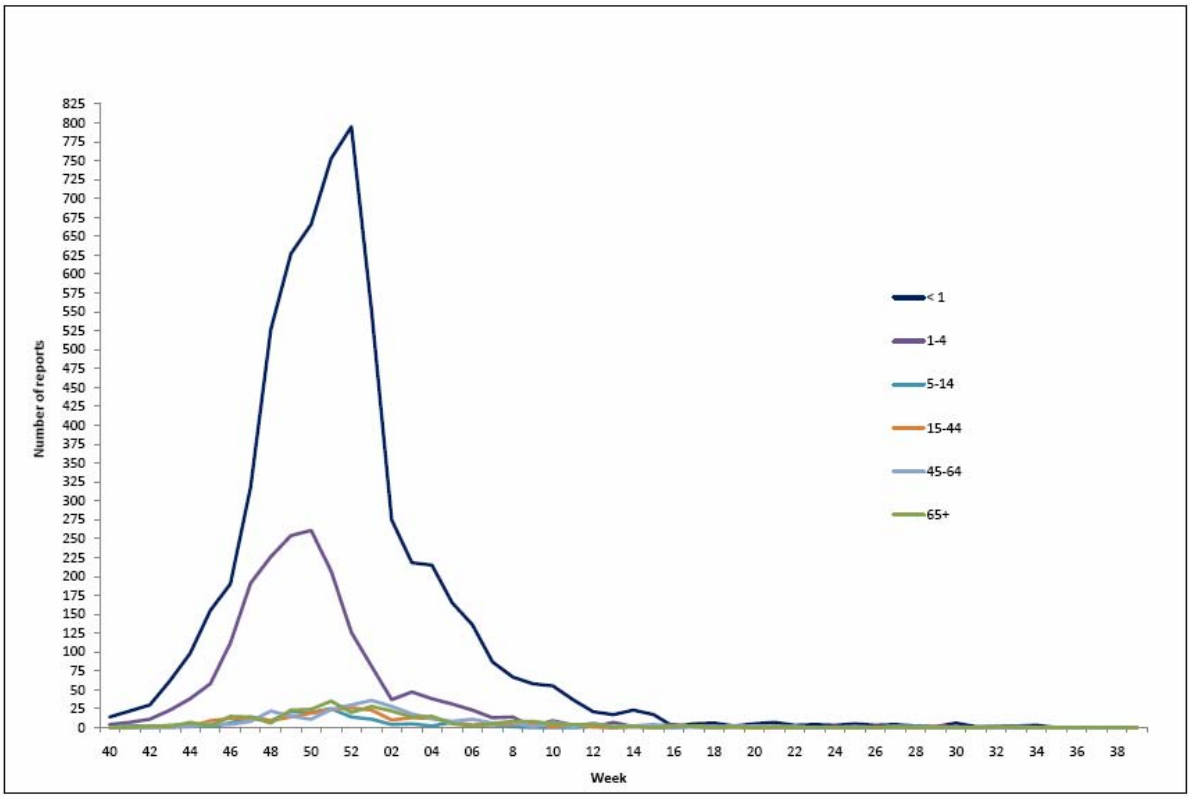


**Figure 1b:** Laboratory reports of RSV by date of specimen (week) and age, 2009 –2010 [Source: Health Protection Agency[5]]

6. The first Health Technology Assessment (HTA) considered by the sub-committee systematically reviewed the available scientific evidence on Palivizumab and assessed the clinical and cost-effectiveness of Palivizumab for the prevention of serious RSV infection in children (Wang *et al*., 2008)[12]. This HTA found that Palivizumab is effective in lowering the risk of serious LRTI caused by RSV infection requiring hospitalisation in high-risk children. However, it is not cost effective if used unselectively in the entire infant population included in the summary of product characteristics.

7. The sub-committee subsequently requested a second HTA to examine the impact of a broader number of potential risk factors, including CHD, CLD, environmental and other factors (including gestational age, male gender, school-age siblings, multiple births, exposure to passive smoke, overcrowding in the family home and parental education). This second HTA (Wang *et al*., *in press)*[13], which was based on the first HTA and included an updated systematic review of the available scientific evidence, assessed the cost-effectiveness of Palivizumab prophylaxis to prevent serious RSV infection in subgroups of infants with different combinations of risk factors. This second HTA provided the basis of the sub-committee's recommendations for the cost-effective use of Palivizumab.

8. The methodology used within both HTAs to assess cost effectiveness was that used by the National Institute for Health and Clinical Excellence (NICE). Both underwent independent peer-review commissioned by the National Institute for Health Research (the sponsor of both HTAs).

9. In considering the HTAs, the sub-committee noted that there are large uncertainties in estimating the cost effectiveness of Palivizumab prophylaxis to prevent serious RSV infection. As a consequence the cost effective estimates derived are imprecise. Uncertainties in the estimates arise because data to assess the impact of risk factors for RSV infection are limited both in terms of quality and number. However, better data would be difficult to acquire. Furthermore, it is likely that risk factors for RSV infection are likely to interact. However, as data are too limited to allow potential interactions to be determined and quantified, it is not possible to make firm conclusions about their impact on the analysis nor about the most appropriate way to model these interactions in the HTA. For these reasons, the sub-committee regarded cost effectiveness estimates based on scenarios where several risk factors are combined to be highly unreliable and concluded that such estimates could not be used to support recommendations for the use of Palivizumab.

10. The sub-committee considered that recommendations on the use of Palivizumab should be practical, proportional and made where there is confidence that use is cost effective. Therefore scenarios based on a small number of risk factors (birth age at the start of the RSV season, gestational age and either CLD or CHD) using a best estimate cost effectiveness threshold of close to £30k per Quality Adjusted Life Year (QALY) could indicate cost effective use of Palivizumab. The sub-committee noted that it is likely that many of such children treated would have additional risk factors that would be likely to make the treatment more cost effective, although the extent is difficult to quantify.

11. Following a review of the evidence and on the basis of the evidence, the sub-committee concluded that the use of Palivizumab to prevent hospitalisation arising from RSV infection is not cost effective in children born at term, neither is its use cost effective for pre-term infants without chronic lung disease (CLD) or congenital heart disease (CHD).

12. However, use of Palivizumab is cost effective and is recommended for pre-term infants with CLD (defined as oxygen dependency for at least 28 days from birth) at the chronological ages at the start of the RSV season and gestational ages at birth covered within the shaded area in Table 1.

Table 1 – Cost effective use of Palivizumab (shaded area) for pre-term infants with CLD by chronological age (months) at the start of the RSV season (beginning of October) and gestational age at birth (weeks). The definition of CLD is oxygen dependency for at least 28 days from birth.

| | Gestational age at birth (weeks) | | | | | | |
|---|---|---|---|---|---|---|---|
| Chronological age (months) | ≤24 | 24-26 | 26-28 | 28-30 | 30-32 | 32-34 | ≥35 |
| 1.0 to <1.5 | | | | | | | |
| 1.5-3 | | | | | | | |
| 3-6 | | | | | | | |
| 6-9 | | | | | | | |
| >9 | | | | | | | |

13. Use of Palivizumab is also cost effective and is recommended for pre-term infants with haemodynamically significant, acyanotic CHD at the chronological ages at the start of the RSV season and gestational ages covered within the shaded area in Table 2.

Table 2 – Cost effective use of Palivizumab (shaded area) for pre-term infants with haemodynamically significant acyanotic CHD by chronological age (months) at the start of the RSV season (beginning of October) and gestational age at birth (weeks)

| | Gestational age at birth (weeks) | | | | | | |
|---|---|---|---|---|---|---|---|
| Chronological age (months) | ≤24 | 24-26 | 26-28 | 28-30 | 30-32 | 32-34 | ≥35 |
| <1.5 | | | | | | | |
| 1.5-3 | | | | | | | |
| 3-6 | | | | | | | |
| 6-9 | | | | | | | |
| >9 | | | | | | | |

14. The sub-committee also considered expert clinical opinion on Palivizumab prophylaxis for two other small groups of children that were not considered in the HTA.

It advised that Palivizumab should be given during the RSV season to children under the age of 24 months who have severe combined immunodeficiency syndrome (SCID), until immune reconstituted. SCID is the most severe form of inherited deficiency of immunity. Affected infants are unable to mount either T-cell responses or produce antibody against infectious agents.

In addition, Palivizumab should be given to Long Term Ventilated (LTV) children aged less than 12 months at the start of the RSV season and LTV children aged less than 24 months with additional co-pathology (heart disease/pulmonary hypertension, intrinsic lung disease (as reflected by oxygen dependency)) at the start of the RSV season. The definition of LTV is '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'[14].

15. The sub-committee also considered the operational use of Palivizumab in terms of the number and timing of the doses given and the circumstances when treatment should begin. It concluded that five doses of Palivizumab should be given one month apart (as stated in the summary of product characteristics for Palivizumab[11]) from the beginning of the RSV season. However, where the course of treatment begins later in the RSV season (e.g. where infants are born within the RSV season) up to five doses should be given one month apart but doses need not be given after the end of

calendar week 8 (end of February). As the risk to an infant of acquiring RSV infection in a Neonatal Unit is extremely low, Palivizumab treatment could begin 24-48 hours before being discharged from hospital for those for whom treatment is cost effective as identified in Tables 1 & 2 above. Infants who have begun a course of Palivizumab treatment but are subsequently hospitalised should continue to receive Palivizumab whilst they remain in hospital.

16. Based on epidemiological data on the timing and duration of RSV infections in previous years (see Figure 1a), the sub-committee considered that for operational purposes the RSV season should be defined as starting at the beginning of calendar week 40 (beginning of October) and ending at the end of calendar week eight (end of February) each year.

## Summary

17. Palivizumab prophylaxis for the prevention of serious RSV infection is recommended by JCVI for groups of infants defined in tables 1 and 2 above as there is reasonable evidence that its use in these groups is cost effective. These recommendations do not preclude use of Palivizumab during the RSV season outside these groups where clinical judgement of individual patient circumstances strongly suggests that Palivizumab would prevent serious RSV infection in infants who are at particular risk of complications from RSV. JCVI identified two other groups where Palivizumab treatment should be considered by clinicians: young children who have severe combined immunodeficiency syndrome (SCID), until immune reconstituted; and young Long Term Ventilated (LTV) children (as defined in paragraph 14).

# Appendix A
# Published papers considered by JCVI

American Academy of Pediatrics, 2009[15]
Broughton S, Roberts A *et al*, 2005[16]
Clark SJ, Beresford MW *et al*, 2000[17]
Duppenthaler A, Ammann RA, *et al*, 2004[18]
Embleton ND, Harkensee C, *et al*, 2005[19]
Feltes TF, Cabalka AK, *et al*, 2003[9]
Fleming DM, Pannell RS, *et al*, 2005[20]
Greenough A, Cox S, *et al*, 2001[21]
Greenough A, Alexander J, *et al*, 2004[22]
Harkensee C, Brodlie M, *et al*, 2006[7]
Health Protection Agency, 2010[4,5]
Krilov LR, Weiner LB, *et al*, 2009[23]
Meissner HC, Bocchini JA, 2009[24]
Nuijten MJ, Wittenberg W, *et al*, 2007[25]
Rackham OJ, Thorburn K, *et al*, 2005[26]
Sigurs N, Gustafsson PM, *et al*, 2005[27]
Simoes EA, Groothuis JR, *et al,* 2007[28]
Simon A, Ammann RA, *et al,* 2007[29]
Thomas M, Bedford-Russell A, *et al*, 2000[30]
Wang D, Cummins C, *et al*, 2008[12]
Wang D, Uthman O *et al*, *In press*[13]

The sub-committee considered other unpublished papers and reports (as described in the minutes of the sub-committee's meetings).

# Appendix B
# References


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