

# 27a

## Respiratory syncytial virus

### The disease

Respiratory syncytial virus (RSV) is an enveloped RNA virus that belongs to the *Paramyxoviridae* family within the Pneumovirus genus. The virus has a non-segmented, single stranded, negative sense genome that encodes 11 proteins. Two surface glycoproteins on the virus (G and F) have important functions for helping the virus bind and fuse to cells. Glycoprotein G binds the virus to a host cell and F fuses the viral envelope with the host cell's plasma membrane, so the virus can enter the host cell. The F protein also stimulates the fusion of the plasma membranes of the infected cells that results in the characteristic 'syncytial' pattern observed in tissue culture. Two major subtypes (A and B) of RSV have been identified based on structural variations in the G protein. The predominance of each subtype changes over successive seasons and is not associated with disease severity. The virus lacks neuraminidase and haemagglutinin surface glycoproteins that are present in the influenza virus (Black, 2003).

RSV is a common cause of respiratory tract infections. It usually causes a mild self-limiting respiratory infection in adults and children, but it can be severe in infants who are at increased risk of acute lower respiratory tract infection. RSV is best known for causing bronchiolitis in infants.

RSV is highly communicable but humans are the only known reservoir. The incubation period varies from two to eight days. The virus is spread from respiratory secretions through close contact with infected persons via respiratory droplets or contact with contaminated surfaces or objects. By two years of age, nearly all children have been infected by RSV at least once (Henderson *et al.*, 1979). Previous infection by RSV may only confer partial immunity to RSV and so individuals may be infected repeatedly with the same or different strains of RSV (Oshansky *et al.*, 2009).

Predisposing factors for RSV infection include prematurity, cardiopulmonary disease, immunodeficiency, and may also include other factors such as

tobacco exposure, day care attendance, overcrowding, lack of breastfeeding, and admission to hospital during the RSV season. Those infected by RSV experience a range of symptoms such as rhinitis (runny nose, sneezing or nasal congestion), cough, shortness of breath, fever, lethargy and decreased appetite. Symptoms can progress to croup, bronchiolitis and acute lower respiratory tract infection. Ear infections may also occur in children (Black, 2003). It has been suggested that RSV infection may be associated with short- or long-term complications that include respiratory complications such as apnoea and hypoxemia, cardiovascular abnormalities, and bacterial infections (Leung *et al.*, 2005). Children who have RSV bronchiolitis in early life may be at increased risk of developing asthma later in childhood, and at increased risk of recurrent wheezing (Sigurs *et al.*, 2005). Those most at risk of developing severe, and occasionally fatal, RSV infection are very young infants born prematurely who have predisposing conditions such as chronic lung disease (CLD), congenital heart disease (CHD) or children who are immunodeficient (Wang *et al.*, 2008).

## History and epidemiology of the disease

RSV infection is a clearly identified winter virus (Public Health England 2013), usually occurring in the UK within the period October to March with most infections occurring in a relatively short epidemic of about six weeks. Whilst the occurrence of the mid-winter peak is predictable, its size varies from year to year (Figures 1 and 2).

Public Health England monitors levels of RSV activity in England and Wales and publishes information throughout the RSV season. The epidemiological data are included in the PHE *Weekly National Influenza Reports* (<https://www.gov.uk/government/statistics/weekly-national-flu-reports>) and the data also appears in the weekly *Health Protection Report* (<https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports>).

RSV surveillance data are gathered from hospital-based microbiology laboratory reports. The vast majority of specimens received for RSV testing are from children aged under one year, followed by those aged between one and four (Figure 3) (Public Health England 2013). Some data on RSV are also gathered as part of the Royal College of General Practitioners community based surveillance scheme of influenza-like illness.

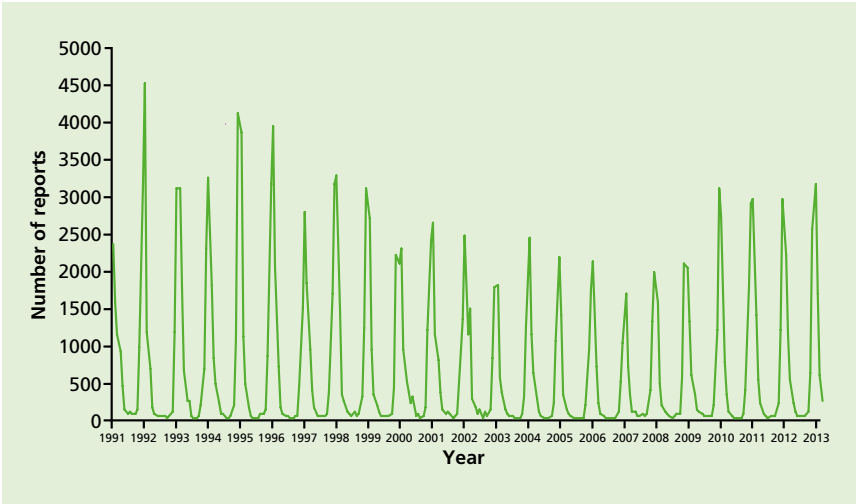


Figure 1 Laboratory reports received by HPA Colindale of infections due to respiratory syncytial virus, England and Wales by date of report 1991-2013 (4 weekly)

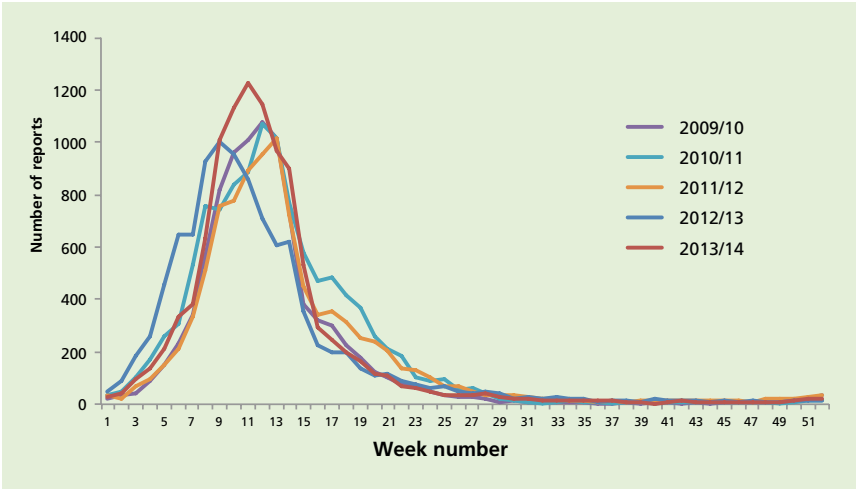


Figure 2 Laboratory reports of RSV received by HPA Colindale from NHS and HPA microbiology laboratories by date of specimen, 2013/14 and recent years

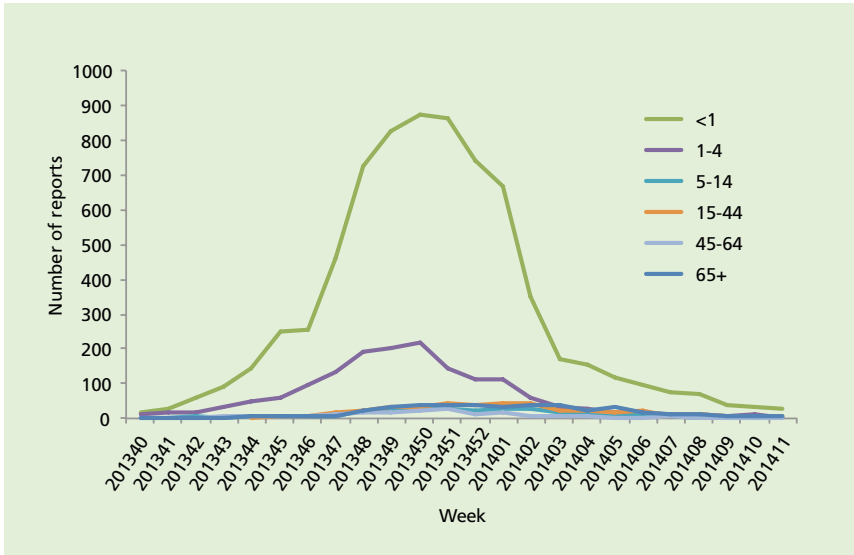


Figure 3 Laboratory reports of RSV received by HPA Colindale from NHS and HPA laboratories, by date of specimen and age, 2013/14

Bronchiolitis is a common cause of hospitalisation in children aged under one year; about one to three per cent of RSV infected children require hospitalisation. In ‘high-risk’ children the mortality rate is about three per cent (Müller-Pebody *et al.*, 2002). Pre-existing conditions, especially cardiac abnormalities and multiple co-morbidities, are associated with a significantly higher risk of death from severe RSV infection (Thorburn, 2009). RSV-associated mortality is highest in developing countries, but RSV can have a significant burden on the cost of care and the economy of all countries (Greenough *et al.*, 2004; Nair *et al.*, 2010).

## The RSV passive immunisation

### Synagis®

Synagis® solution for injection (Palivizumab) is a humanised monoclonal antibody (IgG11K) produced using recombinant DNA techniques in mouse myeloma host cells. It provides passive immunity against RSV. Palivizumab is directed against an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Thus, the antibody targets the F protein of RSV that is responsible for fusing the virus and the host cell and therefore inhibits the virus from entering the host cell (Johnson *et al.*, 1997, Harkensee *et al.*, 2006). This passive immunisation has been shown to be safe and effective in reducing

RSV hospitalisation rates and serious complications among high-risk children (Impact-RSV Study Group, 1998; Feltes *et al.*, 2003). Palivizumab has a half-life in the body in the range of 18 to 21 days. Monthly administration during the RSV season is required to maintain its concentration at a protective level (Johnson, 1997).

Synagis® solution for injection is the only licensed form of Palivizumab available in the UK. The summary of product characteristics (SPC) (Electronic Medicines Compendium, 2015) states that it is indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in the following children at high risk for RSV disease, i.e.:

- children born at 35 weeks or less of gestation and under six months of age at the onset of the RSV season
- children under two years of age and requiring treatment for bronchopulmonary dysplasia within the previous six months
- children under two years of age and with haemodynamically significant congenital heart disease.

The JCVI recommendations are under the ‘Recommendations for the use of the passive immunisation’ section.

### Storage

Synagis® solution for injection should be stored in the original packaging at +2°C to +8°C and protected from light. It needs to be handled in a similar way to vaccines, all of which are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause loss of potency and can also cause hairline cracks in the container, leading to contamination of the contents.

### Presentation

Synagis® solution for injection is a clear or slightly opalescent liquid, supplied in either 0.5 ml or 1.0 ml vials. The concentration of palivizumab in each vial size is 100mg/ml. The vials contain an overfill to allow the withdrawal of 50 mg or 100 mg of liquid Palivizumab from the 0.5ml or 1.0 ml vials respectively. Liquid palivizumab should not be diluted and vials should not be shaken.

## Dosage and schedule

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 (calendar week 40). Subsequent doses should be administered monthly throughout the RSV season up to a maximum of five doses.

## Administration

Synagis<sup>®</sup> solution for injection is given by intramuscular injection, preferably in the anterolateral aspect of the thigh. It can be given at the same time as vaccines administered as part of the routine childhood immunisation programme. The vaccines should be given at separate sites, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each injection is given and the batch numbers of the immunisations should be recorded in the individual's records.

The summary of product characteristics for Synagis<sup>®</sup> states that 'No formal interactions studies with other medicinal products were conducted, however no interactions have been described to date. In the phase III Impact-RSV study in the premature and bronchopulmonary dysplasia paediatric populations, the proportions of patients in the placebo and palivizumab groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.'

## Disposal

Equipment used for prophylaxis, including used vials, ampoules, or partially discharged product should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in the technical memorandum 07-01 (Department of Health, 2006).

## Recommendations for the use of the passive immunisation

The objective of the passive immunisation is to protect at-risk infants for whom RSV infection is likely to cause serious illness or death, and all children less than 24 months of age with severe combined immunodeficiency syndrome (SCID). Based on an analysis of the cost effective use of Palivizumab prophylaxis, Synagis<sup>®</sup> is recommended for use in all children in the following groups.

### 1. High Risk due to Bronchopulmonary dysplasia (BPD) – (also known as chronic lung disease)

- a) Pre-term infants who have moderate or severe BPD. Moderate or severe BPD is defined as ‘preterm infants with compatible x-ray changes who continue to receive supplemental oxygen or respiratory support at 36 weeks post-menstrual age<sup>1</sup>. Children who fall into the **light** and **dark** green shaded area of Table 1 should be offered prophylaxis
- b) Infants with respiratory diseases who are not necessarily pre-term but who remain in oxygen at the start of the RSV season are also considered to be at higher risk

These infants may include those with conditions including:

- pulmonary hypoplasia due to congenital diaphragmatic hernia
- other congenital lung abnormalities (sometimes also involving congenital heart disease or lung malformation)
- interstitial lung disease

**and** including those receiving long term ventilation at the onset of the season.<sup>2</sup>

### 2. High Risk due to Congenital Heart Disease (CHD)

- a) Preterm infants with haemodynamically significant, acyanotic CHD at the chronological ages at the start of the RSV season and gestational ages at birth covered within the **light** green shaded area in Table 1.
- b) Cyanotic or acyanotic CHD **plus** significant co-morbidities particularly if multiple organ systems are involved.

### 3. High Risk due to Severe Combined Immunodeficiency Syndrome (SCID)

- a) Children less than 24 months of age with SCID - the most severe form of inherited deficiency of immunity, who are unable to mount either T-cell responses or produce antibody against infectious agents – until immune reconstituted.

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1 Post-menstrual age is calculated by adding the time elapsed between the first day of the last menstrual period to the day of delivery plus the time elapsed from birth.

2 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’ (Jardine and Wallis, 1998)

Table 1 – Cost effective use of Palivizumab (shaded area)

Chronological age (months)	Gestational age at birth (weeks+days)						
	≤24 <sup>+0</sup>	24 <sup>+1</sup> to 26 <sup>+0</sup>	26 <sup>+1</sup> to 28 <sup>+0</sup>	28 <sup>+1</sup> to 30 <sup>+0</sup>	30 <sup>+1</sup> to 32 <sup>+0</sup>	32 <sup>+1</sup> to 34 <sup>+0</sup>	≥34 <sup>+1</sup>
<1.5							
1.5 to <3							
3 to <6							
6 to <9							
≥9							

Where clinical judgement of other individual patient circumstances strongly suggests that prophylaxis would prevent serious RSV infection in infants who are at particular risk of complications from RSV, use of Synagis® could be considered during the RSV season.

Synagis® should be given as a maximum of five doses given one month apart from the beginning of the RSV season (beginning of calendar week 40 i.e. beginning of October). 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 until the end of calendar week 8 (i.e. the end of February). As the risk of acquiring RSV infection while in the neonatal unit is extremely low, infants in neonatal units who are in the appropriate risk groups should only begin Synagis® treatment 24 to 48 hours before being discharged from hospital. Those infants that have begun a course of Synagis® treatment but are subsequently hospitalised should continue to receive Synagis® whilst they remain in hospital.

Synagis® provides short-term protection against RSV and is recommended to all new at risk infants at the start of each new RSV season (as described above). If, during the RSV season, an infant is identified to be at risk but there is no reliable history of previous Synagis® prophylaxis within the season, then doses should be started and administered monthly for the remainder of the RSV season but need not be given after the end of calendar week 8. Where courses have been interrupted the doses should be restarted and administered monthly for the remainder of the RSV season but need not be given after the end of calendar week 8.



## Contraindications

There are very few infants and children who cannot receive Synagis®. Where there is doubt, appropriate advice should be sought from a specialist.

Synagis® should not be given to infants or children who have had:

- a confirmed anaphylactic reaction to a previous dose of Synagis®
- a confirmed anaphylactic reaction to any components of Synagis®
- a confirmed anaphylactic reaction to another humanised monoclonal antibody.

## Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered.

## Adverse reactions

Anyone can report a suspected adverse reaction to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

The safety of the product was assessed in controlled clinical studies after administration of Synagis®. Common reactions reported included redness or swelling at the injection site, fever, diarrhoea and nervousness. The majority of reactions were transient and mild to moderate in severity. Events reported voluntarily during post-market experience include thrombocytopenia, anaphylaxis, convulsion, apnoea and urticaria; but in these cases it is difficult to establish the frequency and causal relationship to Synagis®. Reports of all adverse reactions can be found in the summary of product characteristics for Synagis® (Electronic Medicines Compendium, 2015).

## Management of cases, contacts and outbreaks

Any case of RSV infection in an at-risk infant or child should prompt a review of the patient's medical history to establish whether they are in a recognised risk group and whether they have been offered prophylaxis. Patients who have risk factors who have not previously been immunised should begin Synagis® prophylaxis.

## Supplies

Synagis® is manufactured by AbbVie and supplies can be obtained in England, Wales and Scotland from AbbVie

(Tel: 0800 783 1699; Fax: 0208 602 1068).

In Northern Ireland supplies can be obtained from Movianto NI

(Tel: 028 90 795799).

## Information materials

The Joint Committee on Vaccination and Immunisation statement on RSV immunisation is available at: [http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@ab/documents/digitalasset/dh\\_120395.pdf](http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_120395.pdf)

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