18a

Respiratory Syncytial Virus (RSV)

Notifiable

In some circumstances, advice in these guidelines may differ from that in the product Summary of Product Characteristics (SmPC). When this occurs, NIAC advises that the recommendations in these guidelines, which are based on current expert advice from NIAC, are followed.

Contents

Key changes

This chapter has been extensively updated and is a rewrite of the previous version.

18a.1 Introduction

Respiratory syncytial virus (RSV) causes annual epidemics during autumn and winter in temperate climates and continues to exert a significant toll on public health and healthcare systems. It is a leading cause of respiratory tract infections and places vulnerable populations, including infants, older adults, and immunocompromised individuals, at increased risk.

Globally RSV is estimated to cause 33 million cases of lower respiratory tract disease (LRTD) per year and 3.6 million hospitalisations in children less than 5 years of age. RSV is the leading cause of infant hospitalisation in Europe.

Almost all infants will have had an RSV infection by two years of age, however those aged less than six months are at highest risk for severe disease. Infection induced immunity is not fully protective and repeated lifelong infections are common. RSV causes a considerable socioeconomic burden, due to the impact of infant infections and hospitalisations on health care systems and caregivers.

RSV is also a significant cause of severe respiratory illness, hospitalisation and death in older adults. Adults aged 60 years and older with medical conditions including chronic lung disease, chronic heart disease, diabetes mellitus, chronic kidney disease and immunocompromising conditions as well as those who are frail or in long term care settings are at greatest risk for RSV-associated hospitalisation.

There are no effective treatments available for RSV infection in either adults or children, supportive care is the mainstay of treatment.

A long-acting monoclonal antibody (Nirsevimab, Beyfortis, Sanofi) and a maternal vaccine (RSVpreF, Abrysvo, Pfizer) have been approved by the European Medicines Agency (EMA) for the prevention of RSV lower respiratory tract disease in infants. A shorter-acting monoclonal antibody (Palivizumab, Synergis, Astra-Zeneca) is also available for use in Ireland in selected high-risk infants. Two vaccines (RSVPreF3, Arexvy,

GSK and RSVpreF, Abrysvo, Pfizer) have been approved by the EMA for the prevention of RSV lower respiratory tract disease in adults aged 60 years and older. (Table 18a.1)

Table 18a.1 Available RSV vaccine and RSV monoclonal antibody products

	RSV vaccine	RSV monoclonal antibody
Infants (<12 months)	· RSVpreF, Abrysvo, Pfizer · Maternal vaccine to protect infants	· Nirsevimab, Beyfortis, Sanofi · Palivizumab, Synergis, Astra-Zeneca
Second year of life		· Nirsevimab, Beyfortis, Sanofi · Palivizumab, Synergis, Astra-Zeneca
Older adults	· RSVPreF3, Arexvy, GSK · RSVpreF, Abrysvo, Pfizer	

These products aim to prevent severe RSV related disease in their target populations, thereby alleviating the associated healthcare burden.

18a.2 Epidemiology

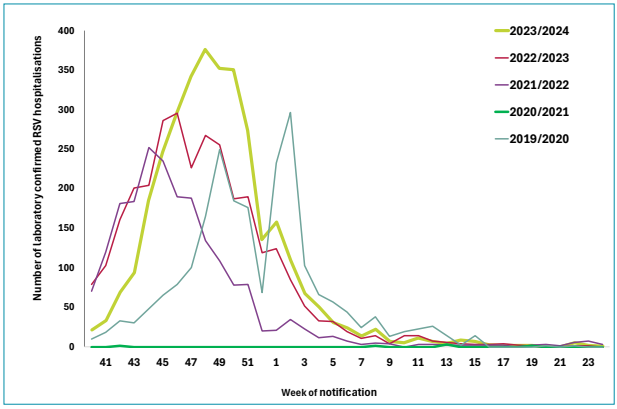
Most infants experience at least one RSV infection by the age of two years with up to 30% of RSV infections occurring in infants aged <6 weeks. While most infections cause only mild symptoms, RSV is the most important cause of viral lower respiratory tract disease (LRTD) in infants and children globally and is responsible for one third of deaths resulting from acute LRTD in the first year of life. In medium and high resource countries, RSV mortality rate in infants is almost nine times that of influenza.

RSV infections typically occur in a seasonal pattern in temperate climates.

Prior to 2021, the RSV season in Ireland, usually began in October and subsided in February. However, in recent years the RSV season has started earlier with cases reported as early as August. In Ireland, as in many other countries, the 2022/2023 and 2023/2024 RSV seasons started earlier, lasted longer and were more severe in terms of case numbers and hospitalisations compared to previous seasons. (Figure 18a.1)

Figure 18a.1 Number of laboratory confirmed RSV notifications (A) and hospitalisations (B) to HPSC by week of notification, 2019/2020 to 2023/2024 season. Source: Ireland's Computerised Infectious Diseases Reporting System

A. Notifications



B. Hospitalisations

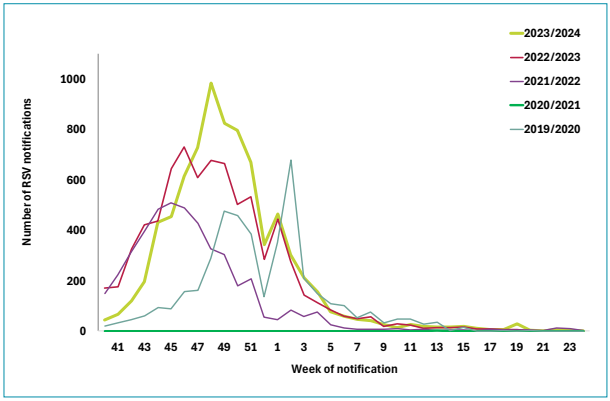
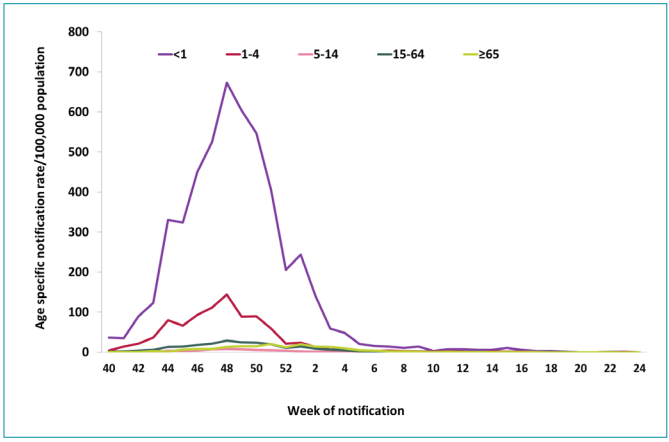


Figure 18a.2 Age specific rates/100,000 population for laboratory confirmed RSV notifications to HPSC by week of notification for the 2023/2024 season. Source: Ireland's Computerised Infectious Disease Reporting System



Those aged less than one year have the highest incidence of hospitalisation from RSV, followed by those aged 1-4 years and those aged 65 years and older. In winter 2023/2024 the age specific incidence rate of hospitalisation per 100,000 for those aged less than one year was 2,474.2, for those aged 1-4 years was 376.7 and for those aged 65 years and older was 71.

Over 500 hospitalisations were reported in those aged 65 years and older in the 2023/2024 season. The incidence of RSV is likely to be underestimated due to under-recognition, undertesting and potentially low sensitivity of standard diagnostic testing among adults.

Table 18.a.2 Number, percentage and rate per 100,000 population of notified laboratory-confirmed RSV hospitalised cases notified in week 20 2024 and the 2023/2024 season (week 40 2023 onwards). Source: Ireland's Computerised infectious Disease Reporting System.

Age (years)	Hospitalised (Week 20 2024)			Season to date (Week 40 2023 - Week 20 2024)		
	Number	% of all Hospitalisations	Rate/100,000 population	Number	% of all Hospitalisations	Rate/100,000 population
<1	0	0.0	0.0	1430	43.2	2474.2
1-4	0	0.0	0.0	895	27.1	376.7
5-14	0	0.0	0.0	189	5.7	26.4
15-24	0	0.0	0.0	29	0.9	4.5
25-34	0	0.0	0.0	31	0.9	4.9
35-44	0	0.0	0.0	39	1.2	4.9
45-54	0	0.0	0.0	50	1.5	7.0
55-64	0	0.0	0.0	94	2.8	16.2
≥65	0	0.0	0.0	551	16.7	71.0
Total	**0**	**100**	**0.0**	**3308**	**100**	**64.2**

Transmission

RSV is highly contagious. Transmission occurs through contact with aerosolised viral particles generated through sneezing and coughing, or from contaminated surfaces or fomites. Large-particle droplets can survive on contaminated surfaces for up to six hours, making handwashing the most effective infection control procedure. The frequent occurrence of mild or asymptomatic infection in otherwise healthy individuals makes infection control challenging.

Incubation period

Incubation is usually 2-8 days.

Infectious period

Infected individuals shed RSV for 3-8 days but immunocompromised patients with severe infection may shed virus for up to four weeks.

18a.3 Effects of RSV

Symptoms of RSV in infants

RSV typically causes a self-limiting upper respiratory tract infection (URTI) with rhinorrhoea, pharyngitis, nasal congestion, coughing, sneezing, tachypnoea, and decreased appetite. Lower respiratory tract disease occurs as bronchiolitis or pneumonia, with fever in <50% of infections, increased work of breathing, hyperinflation, croup (laryngotracheobronchitis), and wheeze. Typically, between 1% and 3% of infected infants require hospitalisation. Treatment is supportive (supplemental oxygen and feeding support).

Symptoms of RSV in adults

For most healthy adults, RSV causes a mild self-limiting cold-like illness. RSV is a significant cause of severe respiratory illness, hospitalisation and death in older adults. Adults over 60 years with medical conditions including chronic lung disease, chronic heart disease, diabetes mellitus, chronic kidney disease and immunocompromising conditions as well as those who are frail or in long term care settings are at greatest risk for RSV-associated hospitalisation.

Diagnosis

RSV can be detected in nasopharyngeal aspirate, bronchoalveolar lavage, sputum, or swabs from the nose and throat by using real-time PCR, immunofluorescence, ELISA and growth in cell culture. PCR is the most sensitive test, and the current gold standard. Detection of viable virus by cell culture and immunofluorescence remain useful to inform infection control measures. Commercially available, easy to perform, point-of-care or near-patient rapid antigen detection tests demonstrate high positive predictive value in an RSV season and are particularly useful to facilitate appropriate isolation precautions and nosocomial outbreak prevention.

18a.4 RSV immunisations

18a.4.1 RSV immunisation for infants and children

Prior to 2022 only one product was available for the prevention of RSV disease in infants; Palivizumab (SmPC), a monoclonal antibody which provides passive immunity against RSV. Palivizumab is a costly intervention which requires administration of five doses, given monthly during the RSV season to maintain protection and is thus recommended only for a cohort of high-risk infants.

In recent years, the characterisation of the RSV fusion glycoprotein (F protein) in its prefusion state has enabled the development of many vaccines and antibody-based therapies for prevention of RSV-induced disease in infants, two of which are now authorised for use in the EU.

18a.4.1.1 Nirsevimab (Beyfortus, Sanofi) (SmPC)

Nirsevimab is a long-acting monoclonal antibody which is administered directly to the infant as a single dose, ideally at the beginning of the RSV season, providing passive immunity against RSV for approximately six months. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion.

Nirsevimab was authorised in the EU in October 2022 for the prevention of RSV lower respiratory tract disease in infants during their first RSV season by administering a single dose at the beginning of the season and to those born during the RSV season. Protection is expected to last approximately five months, similar in duration to an average RSV season.

Storage

Nirsevimab should be stored at +2°C to +8°C. Store in original packaging and protect from light. If Nirsevimab has been frozen it should not be used.

Nirsevimab may be kept at room temperature (+20°C to +25°C) when protected from light for a maximum of 8 hours. After this time, the syringe must be discarded.

Immunogenicity and efficacy

Nirsevimab was authorised by the European Medicines Agency (EMA) based on data from three clinical trials, since authorisation a further pragmatic clinical trial (HARMONIE) was conducted over the 2022/2023 season:

1. MEDLEY trial (phase 2/3) assessed the safety of nirsevimab compared to palivizumab in infants less than 35 weeks' gestation at higher risk for severe RSV disease, including extremely preterm (<29 weeks' gestation), infants with chronic lung disease (CLD) and haemodynamically significant congenital heart disease (CHD). Infants were randomised to receive either nirsevimab (n=616) or palivizumab (n=309).

2. D5290C00003 trial (phase 2b) assessed the safety and efficacy of nirsevimab in preterm infants born between 29 and 35 weeks'

gestation, randomised to receive either nirsevimab (n=969) or placebo (n=484).

3. MELODY (phase 3) trial assessed the safety and efficacy in term and late preterm infants born after 35 weeks' gestation (86% ≥37 weeks' gestation). Infants were randomised to receive either nirsevimab (n=994) or placebo (496).

4. HARMONIE (PHASE 3b) trial assessed safety and efficacy of nirsevimab in healthy infants born after 29 weeks' gestation randomised to receive either nirsevimab (n=4,016) or no intervention (n=4,020).

Immunogenicity and pharmacokinetics

Serum concentrations of nirsevimab decrease linearly over time, with a mean half-life of 69 days. The MEDLEY and MELODY trials found that serum concentrations of nirsevimab were similar at 151 days in preterm, CHD/CLD and term cohorts. Antidrug antibodies (ADAs) were low in these trials, (5.6-6.1% in nirsevimab groups, 1.1-3.8% in treatment groups) and no effect on pharmacokinetics was observed through the first 151 days. However, on day 361 serum nirsevimab concentrations were generally lower in infants with antidrug antibodies compared to those without. In the MELODY trial, infants who had received nirsevimab had RSV neutralising antibodies approximately 50-fold higher at 150 days post-dose compared to baseline pre-dose levels

Efficacy and Effectiveness

In the MELODY Trial, efficacy against medically attended RSV LRTD and hospitalisation was 75% and 62% respectively. In the D5290C0003 trial efficacy against medically attended RSV LRTD and hospitalisation was 70% and 78% respectively. The HARMONIE trial reported an efficacy of 83% efficacy against RSV hospitalisation and a 58% reduction in all cause LRTD hospitalisation.

Early real-world effectiveness data for nirsevimab has been reported in the US and Spain. In the US, effectiveness of nirsevimab was calculated using data from the New Vaccine Surveillance Network (NVSN), a population-based, prospective surveillance platform for acute

respiratory illness (ARI) in infants, children, and adolescents aged <18 years. Infants were eligible for analysis if they were aged <8 months as of October 1, 2023, or born after October 1, 2023, were hospitalised with ARI during October 1, 2023–February 29, 2024, and had verified nirsevimab status. Six hundred and ninety-nine infants across four sites met inclusion criteria. Nirsevimab effectiveness was 90% (95% CI: 75–96) against RSV-associated hospitalisation. This result may not accurately reflect effectiveness in the general population, as due to supply issues in the US, receipt of nirsevimab was more frequent among infants with high-risk medical conditions than those without these conditions (46% versus 6%, p<0.001). Additionally, this is an early estimate, in this analysis, the median interval from receipt of nirsevimab was 45 days. Effectiveness over the full season may be lower due to waning levels of protective antibody over time.

In Catalonia in Spain, a retrospective cohort study, using routinely collected electronic health data from October 1, 2023, to January 31, 2024, included all infants born between April and September 2023. Eighty seven percent of infants received nirsevimab by the end of the study period. The incidence rate of hospital admissions due to RSV bronchiolitis was 9.55 per 100,000 person days for those who did not receive nirsevimab versus 2.16 for those who received nirsevimab. Effectiveness against hospitalisation and ICU admission for bronchiolitis due to RSV was calculated at 87.6% and 90.1% respectively.

In Luxembourg, nirsevimab was recommended to all those born during the RSV season and those born from January 1, 2023. Rates of hospitalisation during the 2022/2023 and 2023/2024 seasons were compared. Uptake of nirsevimab was estimated at 84% (1,277 doses for 1,524 births). There was a reduction of 69% in RSV hospitalisation in infants aged under 6 months (232 vs 72).

Dose, schedule and route of administration

Nirsevimab is for intramuscular injection only and should be administered as follows:

- Infants <5kg: A single dose of 50 mg administered intramuscularly
- Infants ≥5 kg: A single dose of 100 mg administered intramuscularly

- Children up to 24 months entering their second season: 200 mg given as 2 x 100 mg intramuscular injections.

For additional dosing recommendations in those post cardiac surgery requiring cardiopulmonary bypass please consult the SmPC.

Nirsevimab should be administered preferably in the anterolateral aspect of the thigh.

Interchangeability

If an infant has received palivizumab initially they can receive nirsevimab rather than complete the remaining monthly doses of palivizumab. There is no minimum interval between the last dose of palivizumab and the dose of nirsevimab. Given protection from palivizumab wanes after 30 days, nirsevimab should be administered no later than 30 days after the last palivizumab dose, when possible.

Contraindications

- Anaphylaxis to any of the monoclonal antibody constituents listed in the SmPC.
- Serious hypersensitivity reaction to previous immunisation with nirsevimab or palivizumab.

Precautions

- Serious hypersensitivity reactions, including anaphylaxis, have been observed with monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.
- As with any other intramuscular injections, nirsevimab should be given with caution to infants with thrombocytopenia or any coagulation disorder.

Concomitant administration with vaccines

Since nirsevimab is a monoclonal antibody, a passive immunisation specific for RSV, it is not expected to interfere with the active immune response to co-administered vaccines. There is limited experience of co-administration with vaccines. In clinical trials, when nirsevimab was

given with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone. Nirsevimab can be given concomitantly with childhood vaccines. Nirsevimab should not be mixed with any vaccine in the same syringe or vial. When administered concomitantly with injectable vaccines, they should be given with separate syringes and at different injection sites.

Adverse reactions

The most frequent adverse reaction was rash (0.7%) occurring within 14 days post dose. The majority of cases were mild to moderate in intensity. Additionally, pyrexia and injection site reactions were reported at a rate of 0.5% and 0.3% within 7 days post dose, respectively. Injection site reactions were non-serious.

Local:	common: injection site reactions.
General:	common: rash, pyrexia.

18a.4.1.2 Pavilizumab, (Synagis, AstraZeneca) (SmPC)

Pavilizumab a humanized mouse monoclonal antibody specific for the F protein of RSV, provides passive immunity against RSV. It inhibits RSV binding to host cells and prevents fusion of infected cells with adjacent cells. Palivizumab prophylaxis reduces the absolute risk of RSV hospitalisation from about 10% to about 5% for infants born prematurely, for infants with chronic lung disease (CLD), and for infants with haemodynamically significant congenital heart disease (CHD), particularly when complicated by large left-to-right shunts and pulmonary hypertension. It does not reduce the incidence of the need for ventilation or reduce mortality.

Authorised indications: prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease:

- Children born at 35 weeks' gestation or less and aged less than 6 months at the onset of the RSV season.
- Children aged less than 2 years and requiring treatment for bronchopulmonary dysplasia within the last 6 months.
- Children aged less than 2 years and with haemodynamically significant congenital heart disease.

Palivizumab should be stored at +2°C to +8°C. If it has been frozen it should not be used.

Guidelines for use

Differences in epidemiology, practice setting, health care systems and drug cost have resulted in variability in palivizumab recommendations and use nationally and internationally. The following guidance is adapted from the American Academy of Paediatrics. Local Guidelines may be used.

Guidance for palivizumab prophylaxis:

In the first year of life, palivizumab prophylaxis is recommended for:

1. Infants born before 30 weeks, 0 days' gestation.
2. Preterm infants with chronic lung disease (CLD) of prematurity (defined as birth at <32 weeks' gestation and a requirement for >21% oxygen for at least 28 days after birth).
3. Certain infants with hemodynamically significant heart disease, specifically those with acyanotic heart disease requiring medication for congestive cardiac failure and/or moderate to severe pulmonary hypertension, and infants with cyanotic heart disease (in consultation with cardiology specialist).
4. Infants with a pulmonary abnormality or neuromuscular disease that impairs their ability to clear upper airways secretions may be considered for prophylaxis.
5. Children younger than one year who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.

Note: As the risk of acquiring RSV infection in a neonatal unit is extremely low, infants who qualify for prophylaxis should only receive the first dose of palivizumab 24 to 48 hours before discharge. Infants that have begun a course of palivizumab and are subsequently hospitalised should continue to receive prophylaxis whilst in hospital. If a course has been interrupted, doses should be restarted and administered monthly for the remainder of the RSV season.

In the second year of life, palivizumab prophylaxis is recommended for:

- Children with CLD (defined as those who required at least 28 days of supplemental oxygen after birth) and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy) for six months preceding the RSV season.

- Children who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.

Dose, schedule and route of administration
The recommended dose is 15 mg/kg once a month (maximum of 5 doses) during the RSV season. Ideally, the first dose should be administered before the RSV season starts. It can be given at the same time as vaccines administered as part of the Primary Childhood Immunisation Programme.

Contraindications
Anaphylaxis to palivizumab or any component within the product, or to other humanised monoclonal antibodies.

Precautions
Use with caution to patients with thrombocytopenia or any coagulation disorder.

Adverse reactions

Local:	common: injection site reactions.
General:	very common: rash, pyrexia. common: apnoea.

18a.4.2 RSV Maternal vaccination during pregnancy

8a.4.2.1 RSVpreF (Abrysvo, Pfizer) (SmPC)
RSVpreF contains two recombinant stabilised RSV prefusion F antigens representing subgroups RSV-A and RSV-B. Prefusion F is the primary target of neutralising antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated lower respiratory tract disease.

In infants born to mothers who were vaccinated with RSVpreF between weeks 24 and 36 weeks' gestation, protection against RSV-associated lower respiratory tract disease is due to transplacental transfer of RSV neutralising antibodies.

RSVpreF was authorised by the EMA in August 2023 for passive protection against lower respiratory tract disease caused by RSV in infants from birth through six months of age following maternal immunisation during pregnancy.

Immunogenicity and vaccine efficacy
A phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled study was undertaken to assess the efficacy of a single dose of RSVpreF in the prevention of RSV-associated lower respiratory tract disease in infants born to pregnant individuals vaccinated between weeks 24 and 36 of gestation.

RSV-associated lower respiratory tract illness was defined as a medically attended visit with a reverse transcription-polymerase chain reaction (RT-PCR) confirmed RSV illness with one or more of the following: fast breathing, low oxygen saturation (SpO2 <95%) and chest wall indrawing.

RSV-associated severe lower respiratory tract illness was defined as an illness that met the lower respiratory tract illness-RSV criteria plus at least one of the following: very fast breathing, low oxygen saturation (SpO2 <93%), high-flow oxygen supplementation via nasal cannula or mechanical ventilation, ICU admission for >4 hours and/or failure to respond/unconscious.

Vaccine efficacy (VE) was defined as the relative risk reduction of the endpoint in the RSVpreF group compared to the placebo group for infants born to pregnant individuals who received the assigned intervention. There were two primary efficacy endpoints, assessed in parallel, severe RSV-positive medically attended lower respiratory tract illness and RSV-positive medically attended lower respiratory tract illness, occurring within 90, 120, 150 or 180 days after birth.

Vaccine efficacy of RSVpreF against severe medically attended lower respiratory tract illness caused by RSV in infants from birth through six months of age by active immunisation of pregnant individuals ranged from 81.8% (95% CI, 40.6, 96.3) at 90 days after birth to 69.4 % (95% CI, 44.3, 84.1) at 180 days after birth.

Vaccine efficacy of RSVpreF against medically attended lower respiratory tract illness caused by RSV in infants from birth through six months of age by active immunisation of pregnant individuals ranged from 57.1 % (95% CI, 14.7, 79.8) at 90 days after birth to 51.3 % (95% CI, 29.4, 66.8) at 180 days after birth.

Immunogenicity data from the phase 2b SAVVY trial included just over 400 vaccine recipient (73 of whom had received the exact vaccine composition coming to market) and over 100 placebo recipients, vaccinated between 24 and 36 weeks' gestation. The 50% neutralisation geometric mean titres were higher in both maternal and infant samples at birth in vaccine recipients compared to placebo recipients. Geometric mean titre ratio of 2.1 was reported in infants of vaccine recipients compared to infants of placebo recipients. Of note, the levels of RSV neutralising titres in umbilical cord blood did not vary substantially according to gestational age at which the vaccine was administered, supporting a three-month immunisation window. Infant neutralising titres declined over the first six months of life in both groups, while the vaccine recipient group continued to have consistently higher titres compared to the placebo recipients.

Dose, schedule and route of administration
A single dose of 0.5 mL should be administered.

RSVpreF is for intramuscular injection into the deltoid region of the upper arm.

The need for revaccination with a subsequent dose has not been established.

Contraindications
Anaphylaxis to any of the vaccine constituents listed in the SmPC.

Precautions
1. Acute febrile illness, defer until recovery.
2. RSVpreF should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding or bruising may occur following an intramuscular administration to these individuals.

3. The efficacy and safety of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of RSVpreF may be lower in immunosuppressed individuals.
4. RSVpreF has not been studied in pregnant individuals less than 24 weeks' gestation. Since protection of the infant against RSV depends on the transfer of maternal antibodies across the placenta, RSVpreF should be administered between 24 and 36 weeks' gestation.

Adverse reactions

In pregnant women at 24-36 weeks of gestation the most frequently reported adverse reactions were vaccination site pain (41%), headache (31%) and myalgia (27%). The majority of local and systemic reactions in maternal participants were mild to moderate in severity and resolved within 2-3 days of onset.

Local: very common: injection site pain.
common: injection site redness, injection site swelling.

Coadministration

RSVpreF can be administered concomitantly with seasonal quadrivalent influenza vaccine (QIV, surface antigen, inactivated, adjuvanted). In a randomised study in adults aged 65 years and older, the criteria for non-inferiority of the immune responses in the co-administration versus the separate administration group were met. However, numerically lower RSV A and B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed when RSVpreF and inactivated adjuvanted seasonal influenza vaccine were co-administered than when they were administered separately. The clinical relevance of this finding is unknown.

A minimum interval of two weeks is recommended between administration of RSVpreF and administration of a tetanus, diphtheria and acellular pertussis vaccine (Tdap). There were no safety concerns when RSVpreF was co-administered with Tdap in healthy non-pregnant women. Immune responses to RSV A, RSV B, diphtheria and tetanus on co-administration were non-inferior to those after separate administration. However, the immune responses to the pertussis components were lower on co-administration compared to separate

administration and did not meet the criteria for non- inferiority. The clinical relevance of this finding is unknown.

18a.4.3 RSV immunisation for older adults

Two recombinant RSV vaccines have been developed and approved for the prevention of lower respiratory tract disease (LRTD) in individuals aged 60 years and older. Both are subunit vaccines based on prefusion RSV F glycoproteins; however, one includes an AS01E-adjuvant (RSVPreF3, Arexvy) and the other is nonadjuvanted (RSVpreF, Abrysvo).

18a.4.3.1 RSVPreF3 (Arexvy, GSK) (SmPC)

Licensed indications

RSVPreF3 is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults aged 60 years and older.

Immunogenicity and vaccine efficacy

Efficacy against RSV-associated LRTD in adults 60 years and older was evaluated in an ongoing, Phase III, randomised, placebo-controlled, observer-blind clinical study conducted in 17 countries from Northern and Southern Hemispheres. Participants are planned to be followed for up to 36 months.

The primary objective was to demonstrate efficacy in the prevention of a first episode of confirmed RSV-A and/or B associated LRTD during the first season.

Confirmed RSV cases were determined by quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) on nasopharyngeal swab. LRTD was defined based on the following criteria: the participant must have experienced at least 2 lower respiratory symptoms/signs including at least 1 lower respiratory sign for at least 24 hours or experienced at least 3 lower respiratory symptoms for at least 24 hours. Lower respiratory symptoms included: new or increased sputum, new or increased cough, new or increased dyspnoea (shortness of breath). Lower respiratory signs included: new or increased wheezing, crackles/ronchi, respiratory

rate ≥ 20 respirations/min, low or decreased oxygen saturation (O_2 saturation < 95% or ≤ 90% if baseline is < 95%) or need for oxygen supplementation.

Efficacy in preventing first RSV-associated LRTD with an onset from 15 days after vaccination compared to placebo was 82.6% (96.95% confidence interval of 57.9% to 94.1%) in participants aged 60 years and older. Vaccine efficacy against RSV-LRTD was observed through the median follow-up period of 6.7 months. The vaccine efficacy against RSV A-associated LRTD cases and RSV B-associated LRTD cases was 84.6% (95% CI [32.1, 98.3]) and 80.9% (95% CI [49.4, 94.3]), respectively.

Vaccine efficacy was similar against the RSV A and B subtypes and was consistently high among participants aged 60 to 69 years and those aged 70 to 79 years, among prefrail older adults, and among those with coexisting conditions.

In a per-protocol immunogenicity cohort including 1,702 participants between baseline and 1 month after injection, the concentrations or titres in the vaccine group increased by a factor of 13.1 for RSVPreF3-specific IgG antibodies, by a factor of 10.2 for RSV A neutralizing antibodies, and by a factor of 8.6 for RSV B neutralizing antibodies

Dose, schedule and route of administration
RSVPreF3 is administered as a single dose of 0.5 mL.

For intramuscular injection only, preferably in the deltoid muscle.

The need for revaccination with a subsequent dose has not been established.

Contraindications
Anaphylaxis to any of the vaccine constituents listed in the SmPC.

Precautions

- Do not administer the vaccine intravascularly or intradermally. No data are available on subcutaneous administration of RSVPreF3.

- As with other intramuscular injections, RSVPreF3 should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following intramuscular administration to these individuals.

- Safety and immunogenicity data on RSVPreF3 are not available for immunocompromised individuals. Patients receiving immunosuppressive treatment or patients with immunodeficiency may have a reduced immune response to RSVPreF3.

Coadministration
RSVPreF3 may be administered concomitantly with inactivated seasonal influenza vaccines (standard dose unadjuvanted, high dose unadjuvanted, or standard dose adjuvanted).

Upon concomitant administration of RSVPreF3 with seasonal influenza vaccines, numerically lower RSV A and B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed as compared to the separate administration. This was not observed consistently across studies. The clinical relevance of these findings is unknown.

Adverse reactions

Local:	very common: injection site pain. common: injection site erythema, injection site swelling.
General:	very common: headache, myalgia, arthralgia, fatigue. common: fever, chills.

18a.4.3.2 RSVpreF (Abrysvo, Pfizer) (SmPC)
RSVpreF contains two recombinant stabilised RSV prefusion F antigens representing subgroups RSV-A and RSV-B. Prefusion F is the primary target of neutralising antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated lower respiratory tract disease.

Licensed indications
RSVpreF is indicated for:

- Passive protection against lower respiratory tract disease caused by RSV in infants from birth through six months of age following maternal immunisation during pregnancy.
- Active immunisation of individuals aged 60 years and older for the prevention of lower respiratory tract disease caused by RSV.

Immunogenicity and vaccine efficacy

A phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled study assessed the efficacy of RSVpreF in the prevention of RSV-associated lower respiratory tract illness in individuals aged 60 years and older.

RSV-associated lower respiratory tract illness was defined as RT-PCR confirmed RSV illness with two or more or three or more of the following respiratory symptoms within 7 days of symptom onset and lasting more than one day during the same illness: new or increased cough, wheezing, sputum production, shortness of breath or tachypnoea (≥25 breaths/min or 15% increase from resting baseline).

The primary objective was assessment of vaccine efficacy (VE), defined as the relative risk reduction of first episode of RSV-associated lower respiratory tract illness in the RSVpreF group compared to the placebo group in the first RSV season.

Vaccine efficacy of RSVpreF in individuals aged 60 years and older was 65.1 % (95% CI 35.9, 82.0) against first episode of RSV- associated lower respiratory tract illness with ≥2 symptoms and 88.9% (95% CI 53.6, 98.7) against first episode of RSV- associated lower respiratory tract illness with ≥3 symptoms.

Immunogenicity was assessed in a phase 1/2 study of 317 adults aged 65-85 years, 250 of whom received a dose of RSVpreF. Serum RSV A and RSV B neutralising titres were measured up to 12 months post vaccination. RSV A and RSV B neutralising titres were measured with three different vaccine doses of 60 microgram, 120 microgram and 240 microgram. All RSVpreF doses elicited high RSV A and RSV B neutralising antibody geometric mean titres (GMT) at one month post vaccination (geometric mean fold rise ranging from 4.8 to 11.6 and 4.5

to 14.1 respectively). GMTs in all groups declined after month one but remained higher than baseline at 12 months post vaccination.

Dose, schedule and route of administration
A single dose of 0.5 mL should be administered.

RSVpreF is for intramuscular injection into the deltoid region of the upper arm.

The need for revaccination with a subsequent dose has not been established.

Contraindication
Anaphylaxis to any of the vaccine constituents listed in the SmPC.

Precautions

1. Acute febrile illness, defer until recovery.
2. Caution for individuals with thrombocytopenia or any coagulation disorder since bleeding or bruising may occur following IM injection.
3. The efficacy and safety of RSVpreF have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of RSVpreF may be lower in immunosuppressed individuals.
4. RSVpreF has not been studied in pregnant individuals less than 24 weeks' gestation. For transfer of maternal antibodies administer between weeks 24 and 36 weeks' gestation.

Coadministration
RSVPreF can be administered concomitantly with seasonal quadrivalent influenza vaccine (QIV, surface antigen, inactivated, adjuvanted). In a randomised study in adults aged 65 years and older, the criteria for non-inferiority of the immune responses in the

co-administration versus the separate administration group were met. However, numerically lower RSV A and B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed when RSVPreF and inactivated adjuvanted seasonal influenza vaccine were co-administered than when they were administered separately. The clinical relevance of this finding is unknown.

A minimum interval of two weeks is recommended between administration of RSVPreF and administration of a tetanus, diphtheria and acellular pertussis vaccine (Tdap). There were no safety concerns when RSVPreF was co-administered with Tdap in healthy non-pregnant women. Immune responses to RSV A, RSV B, diphtheria and tetanus on co-administration were non-inferior to those after separate administration. However, the immune responses to the pertussis components were lower on co-administration compared to separate administration and did not meet the criteria for non-inferiority. The clinical relevance of this finding is unknown.

Adverse reaction

In individuals aged 60 years and older the most frequently reported adverse reaction was vaccination site pain (11%). The majority of reactions were mild to moderate in severity and resolved within 1-2 days of onset.

Local: very common: injection site pain.
common: injection site redness, injection site swelling.

18a.5 Recommendations for the 2024/2025 RSV season

18a.5.1 RSV immunisation of infants and at risk children in the second year of life

1. NIAC recommends the passive immunisation with nirsevimab of all infants who are born during the RSV season. These infants should receive nirsevimab ideally prior to discharge home from a maternity hospital.

2. NIAC recommends the passive immunisation with nirsevimab of all high risk infants* aged ≤12 months at the start of their first RSV season. These infants should receive nirsevimab prior to the start of the RSV season.

3. NIAC recommends the passive immunisation with nirsevimab of all infants who are aged ≤6 months at the start of the RSV season. These infants should receive nirsevimab prior to the start of the RSV season.

4. NIAC recommends the passive immunisation with nirsevimab of all ex-preterm infants aged under 24 months with chronic lung disease† in their second RSV season. Infants who will be severely immunocompromised during the RSV season may also be considered for nirsevimab in consultation with their treating specialist. These infants should receive nirsevimab prior to the start of the RSV season.

5. In the event of short supply or programmatic limitations youngest infants (those born during the RSV season) and high risk infants* in their first RSV season should be prioritised.

6. Neonates‡ with prolonged hospitalisation from birth due to prematurity or other reasons should receive nirsevimab shortly before discharge from hospital if they are being discharged during or shortly before the RSV season.

7. The RSV season in Ireland typically starts in calendar weeks 38-40 and ends around calendar week 8 of the following year. Assuming the 2024/2025 season follows a similar pattern, the programme should start in late September 2024 and finish at the end of February 2025. If no catch-up program is planned, an earlier start to the programme (September 1st) should be considered to capture those who will be

aged under three months at the peak of the RSV season. The definitive end date for the program should be determined by levels of circulating RSV and may need to be adjusted.

* High risk infants include:

- Infants born before 30 weeks, 0 days' gestation.
- Preterm infants with chronic lung disease (CLD) of prematurity (defined as birth at <32 weeks' gestation and a requirement for >21% oxygen for at least 28 days after birth).
- Certain infants with hemodynamically significant heart disease, specifically those with acyanotic heart disease requiring medication for congestive cardiac failure and/or moderate to severe pulmonary hypertension, and infants with cyanotic heart disease (in consultation with cardiology specialist).
- Infants with a pulmonary abnormality or neuromuscular disease that impairs their ability to clear upper airways secretions may be considered for prophylaxis.
- Children younger than one year who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.

† CLD is defined as those who required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy) for 6 months preceding the RSV season.

‡ Earlier inpatient administration may be considered if infant is considered at risk of RSV exposure in hospital. Dosing in infants with a body weight from 1.0 kg to <1.6 kg is based on extrapolation; no clinical data are available. There is no data to inform dosing in infants <1kg and the benefits and risks of nirsevimab use in infants <1kg should be carefully considered.

18a.5.2 RSV immunisations in adults

1) NIAC recommends RSV vaccination for those aged 65 years and older with either RSVPreF3 (Arexvy, GSK) or RSVpreF (Abrysvo, Pfizer).

Both these products have similar safety and efficacy profiles. Further analysis of cost and product availability is needed to determine which product is more suitable for programmatic use in Ireland.

2) Vaccine administration should aim to take place prior to the anticipated start of the RSV season where possible.

3) In the event of limited supply of vaccines, priority should be given to those of more advanced age, those with significant comorbidities and those living in long term care facilities for older adults as they are at the highest risk of severe RSV disease.

An up-to-date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

A list of the vaccines currently available from the National Cold Chain Service can be found at www.immunisation.ie

Bibliography

Baber J, Arya M, Moodley Y, et al (2022). A Phase 1/2 Study of a Respiratory Syncytial Virus Prefusion F Vaccine With and Without Adjuvant in Healthy Older Adults. The Journal of Infectious Diseases; 226(12):2054-63. doi: 10.1093/infdis/jiac189.

Branche AR, Saiman L, Walsh EE, et al (2022). Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017–2020. Clinical Infectious Diseases; 74(6):1004-11. doi: 10.1093/cid/ciab59.

Childs A, Zullo AR, Joyce NR, et al (2019). The burden of respiratory infections among older adults in long-term care: a systematic review. BMC Geriatrics; 19(1):210. doi: 10.1186/s12877-019-1236-6.

Coma E, Martinez-Marcos M, Hermosilla E et al (2024). Effectiveness of nirsevimab immunoprophylaxis against respiratory syncytial virus-related outcomes in hospital and primary care settings: a retrospective cohort study in infants in Catalonia (Spain). Arch Dis Child; Jun 10:archdischild-2024-327153. doi: 10.1136/archdischild-2024-327153.

Del Riccio M, Spreeuwenberg P, Osei-Yeboah R, et al (2023). Burden of Respiratory Syncytial Virus in the European Union: estimation of RSV-associated hospitalizations in children under 5 years. The Journal of Infectious Diseases :jiad188. doi: 10.1093/infdis/jiad1883.

Domachowske J, Madhi SA, Simões EAF, et al (2022). Safety of Nirsevimab for RSV in Infants with Heart or lung disease or Prematurity. New England Journal of Medicine;386(9):892-94. doi: 10.1056/NEJMc211218628.

Drysdale SB, Cathie K, Flamein F, et al (2023). HARMONIE Study Group. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. N Engl J Med; Dec 28;389(26):2425-2435. doi: 10.1056/NEJMoa2309189. PMID: 38157500.

Ernst C, Bejko D, Gaasch L, et al (2024). Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. Euro Surveill;29(4) doi: 10.2807/1560-7917.Es.2024.29.4.2400033 [published Online First: 2024/01/26]

European Medicines Agency (2024). Abrysvo Summary of Product Characteristics. [Available from: https://www.ema.europa.eu/en/documents/product-information/abrysvo-epar-product-information_en.pdf accessed June 2024].

European Medicines Agency (20024). Arexvy Summary of Product Characteristics [Available from: https://www.ema.europa.eu/en/documents/product-information/arexvy-epar-product-information_en.pdf accessed June 2024].

European Medicines Agency (2024). Beyfortus Summary of Product Characteristics. [Available from: https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf accessed June 2024].

European Medicines Agency (2024). Synagis Summary of Product Characteristics. [Available from: https://www.ema.europa.eu/en/documents/product-information/synagis-epar-product-information_en.pdf accessed June 2024].

Griffin MP, Yuan Y, Takas T, et al (2020). Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. New England Journal of Medicine;383(5):415-25. doi: 10.1056/NEJMoa191355629.

Hammitt LL, Dagan R, Yuan Y, et al (2022). Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. New England Journal of Medicine;386(9):837-46. doi: 10.1056/NEJMoa2110275.

Health Protection Surveillance Centre (HPSC) (2024). Respiratory syncytial virus (RSV) surveillance in Ireland. Source: Ireland's Computerised Infectious Diseases Reporting System. [Available at https://respiratoryvirus.hpsc.ie/pages/rsv accessed June 2024]

Kampmann B, Madhi SA, Munjal I, et al (2023). Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. New England Journal of Medicine;388(16):1451-64. doi: 10.1056/NEJMoa2216480.

Kujawski SA, Whitaker M, Ritchey MD, et al (2022). Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure—United States, 2015–2017. PLOS ONE;17(3):e0264890. doi: 10.1371/journal.pone.02648907.

Leroux-Roels I, Davis MG, Steenackers K, et al (2022). Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomized Clinical Trial. The Journal of Infectious Diseases;227(6):761-72. doi: 10.1093/infdis/jiac327.

Li Y, Wang X, Blau DM, et al (2022). Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. The Lancet;399(10340):2047-64. doi: 10.1016/S0140-6736(22)00478-02.

McLellan JS, Chen M, Leung S, et al (2013). Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. Science;340(6136):1113-7. doi: 10.1126/science.1234914 [published Online First: 20130425]

Moline HL, Tannis A, Toepfer AP, et al (2024). Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus-Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Virus Season -New Vaccine Surveillance Network, October 2023-February 2024. MMWR;73(9):209-14. doi: 10.15585/mmwr.mm7309a4 [published Online First: 2024/03/08]7.

National Immunisation Guidelines of Ireland (2019). Respiratory Syncytial Virus, Chapter 18a. [Available from: https://rcpi.access.preservica.com/uncategorized/IO_bc30709d-43db-4dc5-a802-97cd426eb59b/ accessed June 2024].

Onwuchekwa C, Moreo LM, Menon S, et al (2023). Underascertainment of Respiratory Syncytial Virus Infection in Adults Due to Diagnostic Testing Limitations: A Systematic Literature Review and Meta-analysis. J Infect Dis;228(2):173-84. doi: 10.1093/infdis/jiad012.

Papi A, Ison MG, Langley JM, et al (2023). Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. New England Journal of Medicine;388(7):595-608. doi: 10.1056/NEJMoa220960450.

Peterson JT, Zareba AM, Fitz-Patrick D, et al (2022). Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F Vaccine When Coadministered with a Tetanus, Diphtheria, and Acellular Pertussis Vaccine. J Infect Dis;225(12):2077-86. doi: 10.1093/infdis/jiab50527.

Ramirez J, Carrico R, Wilde A, et al (2023). Diagnosis of Respiratory Syncytial Virus in Adults Substantially Increases When Adding Sputum, Saliva, and Serology Testing to Nasopharyngeal Swab RT-PCR. Infect Dis Ther;12(6):1593-603. doi: 10.1007/s40121-023-00805-1 [published Online First: 20230506].

Simões EAF, Center KJ, Tita ATN, et al (2022). Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy. New England Journal of Medicine;386(17):1615-26. doi: 10.1056/NEJMoa2106062.

Walsh EE, Pérez Marc G, Zareba AM, et al (2023). Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. New England Journal of Medicine;388(16):1465-77. doi: 10.1056/NEJMoa221383654.

Wyffels V, Kariburyo F, Gavart S, et al (2020). A Real-World Analysis of Patient Characteristics and Predictors of Hospitalization Among US Medicare Beneficiaries with Respiratory Syncytial Virus Infection. Advances in Therapy;37(3):1203-17. doi: 10.1007/s12325-020-01230-3.

Young M, Smitherman L (2021). Socioeconomic Impact of RSV Hospitalization. Infect Dis Ther;10(Suppl 1):35-45. doi: 10.1007/s40121-020-00390-7 [published Online First: 20210303].