



National Immunisation Advisory Committee

RECOMMENDATIONS FOR PASSIVE IMMUNISATION AND VACCINATION AGAINST
RESPIRATORY SYNCYTIAL VIRUS IN INFANTS, CHILDREN AND OLDER ADULTS

NIAC | 12.10.2023

About NIAC

NIAC membership includes nominees from the Royal College of Physicians in Ireland, its Faculties and Institutes, the Royal College of Surgeons in Ireland, the Irish College of General Practitioners, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are attended by representatives from the Department of Health and the HSE. Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

[NIAC](#) considers the evidence about vaccines and provides advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the Health Service Executive.

RECOMMENDATIONS FOR RSV PASSIVE IMMUNISATION AND VACCINATION

1. INFANTS AND CHILDREN

- a) NIAC recommends the passive immunisation of all infants against RSV during their first RSV season.

Two forms of passive immunisation for infants against RSV have recently been authorised in the EU; a long-acting monoclonal antibody (nirsevimab) which can be administered to the infant directly, and a maternal vaccine RSVpreF (Abrysvo, Pfizer) which can provide infant protection through transplacental antibody transfer. Both products have acceptable safety and efficacy profiles. Further analysis of cost effectiveness and programmatic considerations is required to determine the most appropriate RSV passive immunisation strategy for Irish infants.

- b) Once available, nirsevimab should replace palivizumab for those high-risk infants and children who are currently eligible to receive palivizumab.

2. OLDER ADULTS

- a) 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 use in Ireland.

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

Recommendations may be updated if more information becomes available

1. EXECUTIVE SUMMARY

Background

- Respiratory syncytial virus (RSV) is a highly transmissible virus which causes annual epidemics during autumn and winter in temperate climates.
- RSV is the leading cause of respiratory infection in children under five years of age, with the most severe manifestations in those less than six months of age, those born prematurely and those with congenital heart disease, chronic lung disease, immunocompromise, respiratory or neuromuscular disorders.
- For most children RSV causes a cold-like illness, however it can progress to bronchiolitis and pneumonia requiring hospitalisation for supportive care and mechanical ventilation.
- For the majority of healthy adults, RSV causes a mild self-limiting cold-like illness. Older adults and adults with co-morbidities including chronic pulmonary disease, chronic cardiac conditions, cerebrovascular disease, chronic kidney disease and other immunocompromising conditions are at increased risk of severe lower respiratory tract disease, hospitalisation and death from RSV.

Epidemiology

- In Ireland, as in many other countries, the 2022/2023 RSV season was more severe than previous years in terms of case numbers and hospitalisations.
- Prior to 2021 the RSV season usually began in Ireland in October and subsided in February, however in recent years the RSV season has started earlier with cases reported as early as August.
- Those aged less than one year of age have the highest incidence and hospitalisation rates followed by those aged 1-4 years and then those aged 65 years and above.
- Infant RSV infection poses a significant burden on paediatric services in Ireland. In 2021 there were over 2000 RSV related admissions in children under two years of age.
- While infants with comorbidities are at higher risk of severe RSV disease, most infants hospitalised with RSV do not have additional risk factors for severe disease.
- An estimated 3-19% of infants hospitalised with RSV require paediatric intensive care unit (PICU) admission.
- RSV monoclonal antibody prophylaxis (passive immunisation) with palivizumab is currently offered to infants at highest risk of severe RSV disease, such as those born at less than 30 week's gestation, those with chronic lung disease of prematurity and those with haemodynamically significant cardiac disease.
- In Ireland between 2010 and 2019, the majority of PICU RSV positive admissions were born at term (37-40 weeks); <7% had received Palivizumab.
- From 50 years of age the risk of severe RSV disease increases incrementally with age, with those aged over 80 years at particularly high risk of hospitalisation, ICU admission and death.

Infant Immunisation

- Two forms of passive immunisation for infants against RSV have recently been authorised in the EU; a long-acting monoclonal antibody (nirsevimab) which can be administered to the infant directly, and a maternal RSV vaccine (RSVpreF) which can provide infant protection through transplacental antibody transfer.
- Nirsevimab (Beyfortus, Sanofi) 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. Protection is expected to last approximately 5 months, similar in duration to an average RSV season.
- In two studies comparing nirsevimab to placebo in infants born between 29- and 35-weeks' gestation, and in those born at ≥ 35 weeks' gestation, there were less RSV infected infants requiring medical attention in the nirsevimab groups (2.6% and 1.2% respectively) compared to the placebo groups (9.5% and 5% respectively).
- Preliminary data from a clinical trial conducted in Europe during winter 2022/23 involving over 8,000 infants reported an 83% reduction in RSV related hospitalisations in infants who had received nirsevimab.
- In infants at high risk for severe RSV due to prematurity or congenital heart disease, nirsevimab was found to have a similar safety and efficacy profile to palivizumab.
- For infants eligible to receive palivizumab, nirsevimab is a safe effective alternative which requires four fewer injections, reducing the burden on infants, their families and the healthcare system.
- RSVpreF (Abrysvo, Pfizer) was approved in the EU in August 2023. It is indicated for passive protection against lower respiratory tract disease (LRTD) caused by RSV in infants from birth through six months of age following maternal immunization during pregnancy.
- RSVpreF maternal vaccination has a reported efficacy of 82% against severe medically attended RSV LRTD in infants for the first 90 days of life, and 69% through to six months of life.

Nirsevimab and RSVpreF have similar safety and efficacy profiles. Additional factors, including cost-effectiveness and acceptability will need to be considered to determine the optimal strategy to protect infants.

Older Adult Vaccination

- Two RSV subunit vaccines have been authorised in the EU for the immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease (LRTD) caused by RSV: RSVPreF3 (Arexvy, GSK) and RSVpreF (Abrysvo, Pfizer).
- Clinical trial data on both vaccines show them to be safe and effective at reducing LRTD caused by RSV in adults aged 60 years and older, with higher efficacies reported in both studies against more severe RSV disease (86-94%).

- Preliminary data suggests that both vaccines provide protection against RSV into a second season without revaccination.
- Given the high burden of RSV in older adults in Ireland, both to individuals and to the healthcare system, the introduction of RSV vaccination for those aged 65 or older has the potential to reduce associated morbidity and mortality and relieve pressure on the healthcare system during the busy winter season.

2. INTRODUCTION

Respiratory syncytial virus (RSV) is a linear single-stranded RNA virus. It is a highly transmissible virus with two transmembrane glycoproteins that are involved in viral entry into cells, attachment (G) and fusion (F) glycoproteins.

RSV causes annual epidemics during autumn and winter in temperate climates and continues to exert a formidable 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 heightened risk.

Globally it is estimated to cause 33 million lower respiratory tract infections per year, and 3.6 million hospitalisations in children less than 5 years of age.¹ RSV is the leading cause of infant hospitalisation in Europe.² 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 considerable socioeconomic burden, due to the impact of infant infections and hospitalizations on health care systems and caregivers.³

RSV is a significant cause of severe respiratory illness, hospitalisation and death in older adults.⁴ 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.⁵⁻

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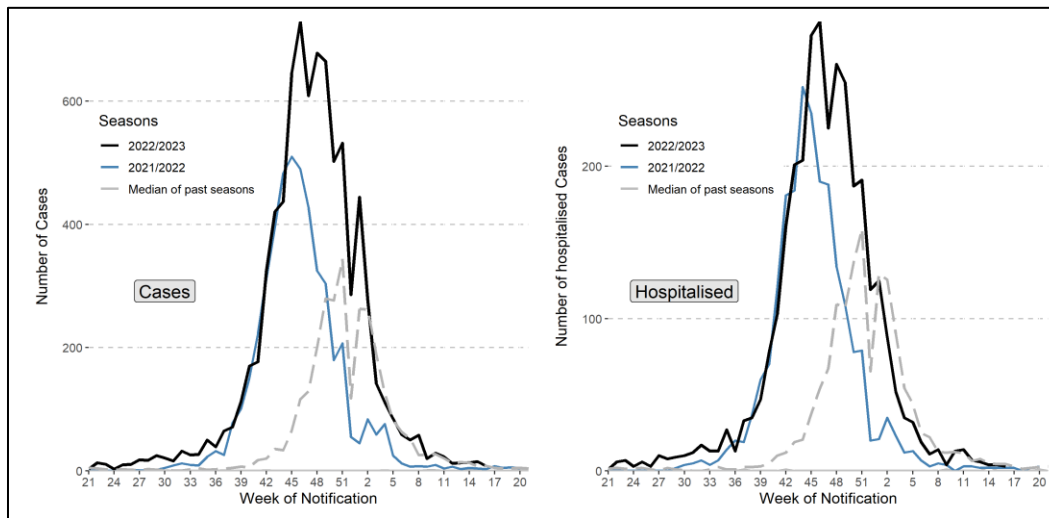
There are no effective treatments available for RSV in either adults or children, supportive care is the mainstay of treatment.

Two new vaccines and a long-acting monoclonal antibody have been approved by the European Medicines Agency (EMA) for the prevention of RSV in infants and older adults. These novel products aim to prevent severe RSV related disease in their target populations, thereby alleviating the associated healthcare burden.

3. EPIDEMIOLOGY

Prior to 2021, the RSV season usually began in Ireland 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 2021/2022 and 2022/2023 RSV seasons started earlier, lasted longer and were more severe in terms of case numbers and hospitalisations compared to previous seasons.⁸ (Figure 1)

Figure 1. Number of notified RSV cases and hospitalisations per week by season up to 27 April 2023. Source: HPSC.⁸



Those aged less than one year of age have the highest incidence of hospitalisation from RSV, followed by those aged 1-4 years and those aged 65 years and above. In winter 2022/2023 the age specific incidence rate of hospitalisation per 100,000 for those aged less than one year was 1,686, for those aged 1-4 years was 266 and for those aged 65 years and above was 107.⁸ (Table 1)

Table 1. Number and age-specific rate per 100,000 of notified RSV cases and RSV hospitalised cases, week 40 2022 to week 20 2023. Source: HPSC.⁸

Age Group	Total Cases	Age Specific Rates	Hospitalised Cases	Age Specific Rates
<1	2266	3639.75	1081	1736.35
1-4	1514	562.29	715	265.54
5-14	373	55.26	152	22.52
15-24	178	30.88	44	7.63
25-34	227	34.42	65	9.86
35-44	253	33.87	58	7.77
45-54	296	47.28	68	10.86
55-64	467	91.76	127	24.95
65-69	288	136.34	88	41.66
70-74	328	202.13	123	75.80
75-79	386	334.29	140	121.25
80+	981	660.20	343	230.83

Infant RSV poses a significant burden on paediatric services in Ireland. In CHI-Crumlin 2,851 inpatient admissions were reported between 2004 and 2018, with a median age of 3-4 months at time of admission. The median length of stay was 4 days, occupying on average 841 inpatient bed days per year. Of those admitted to CHI-Crumlin with RSV, 14% required PICU admission.⁹ This is comparable to international studies which have reported PICU admission rates of 3-19% in infants hospitalised with RSV.¹⁰⁻¹²

From 2010 to 2020 there were 823 RSV related PICU admissions in Ireland. Over 80% of those admitted were less than 12 months of age, the median age at PICU admission was 2 months. The median gestation at birth of PICU admissions was 38 weeks (IQR 36-40 weeks). Of those admitted to PICU, 44.5% had a comorbidity known to increase the risk of severe RSV disease and 6.5% of those admitted to PICU had received palivizumab prior to admission.⁹

RSV causes a significant number of admissions in adults also. Over 800 hospitalisations were reported in those aged 60 years and older in the 2022/2023 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.^{13 14}

4. RSV IMMUNISATIONS FOR INFANTS AND CHILDREN

Prior to 2022 only one product was available for the prevention of RSV disease in infants; Palivizumab. Palivizumab is authorised for the prevention of serious lower respiratory tract disease (LRTD) requiring hospitalisation caused by RSV in children at high risk for RSV disease. In Ireland this is recommended for use in the first year of life for infants born prematurely (before 30 weeks' gestation), those with chronic lung disease (CLD), and those with haemodynamically

significant heart disease, and may be considered in some other high-risk groups (see Chapter 18a).¹⁵ It is also recommended in the second year of life for those with CLD requiring ongoing treatment. Palivizumab is a costly intervention which requires administration of five doses, given monthly during the RSV season to maintain protection.

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.¹⁶ ¹⁷ RSVpreF (Abrysvo, Pfizer) is a maternal RSV vaccine designed to be given as a single dose to pregnant women in the late second or third trimester to optimise the transplacental transfer of antibodies to the infant, providing passive immunity in the first six months of life.¹⁸ Nirsevimab (Beyfortus, Sanofi) 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, again providing passive immunity against RSV for approximately six months.¹⁹

RSVpreF (Abrysvo, Pfizer); Maternal RSV vaccine

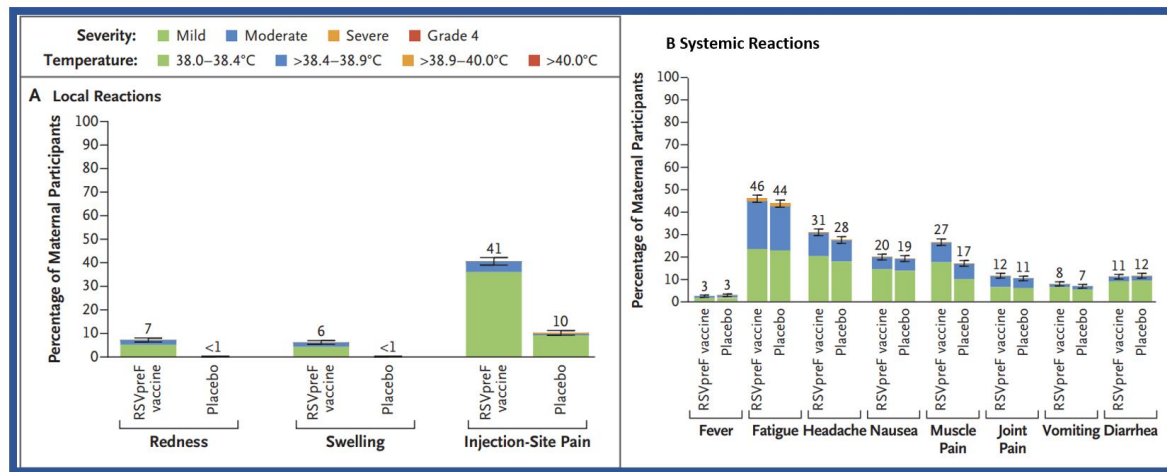
RSVpreF is indicated for passive protection against LRTD caused by RSV in infants from birth through six months of age following maternal immunization during pregnancy.¹⁸

Authorisation was granted based on results of the phase 3 clinical trial, the MATISSE study. This study included over 7,000 pregnant women aged between 18 and 49 years in 18 countries. Participants were randomised 1:1 to receive either RSVpreF or placebo between 24 and 36 weeks' gestation.²⁰

Safety

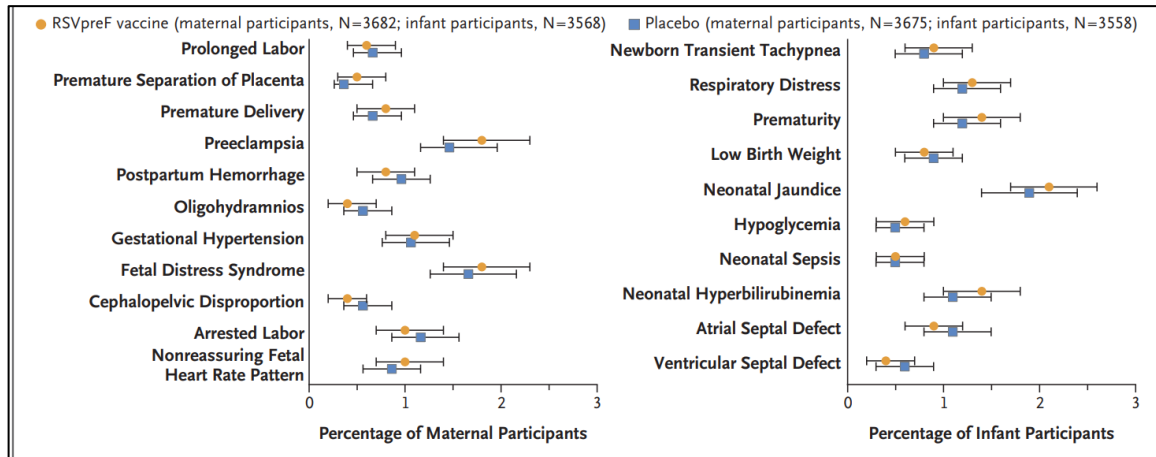
The vaccine was generally well tolerated. The most common side effects reported in those who received the vaccine were injection site pain, fatigue, headache and muscle pain. With the exception of muscle pain (27% vaccine vs 17% placebo group), event rates for other systemic events were similar between the vaccine and placebo groups. In infants, the percentage reporting any adverse event within one month of birth was 37% in the vaccine group and 34% in the placebo group.²⁰ (Figure 2)

Figure 2. Local reactions (A) and systemic events (B) within 7 days of injection. Source adapted from NEJM Kampmann et al.²⁰



The incidence of preterm birth (<34 weeks' gestation) was not statistically different between groups, but a slightly higher number of cases were reported in the vaccine group (28 cases, 0.8%) compared to the placebo group (23 cases, 0.6%).²⁰ (Figure 3) A trial on a similar vaccine from a different manufacturer (GSK) was halted in February 2022 due to a safety signal regarding increased preterm births in the vaccinated cohort.²¹ This prompted a further review of Pfizer's data regarding preterm births in their RSVpreF vaccine trials. It was noted that in high income countries there was no difference in preterm births (less than 37 weeks) between groups (5.1% in both groups), however in upper middle-income countries the difference was more prominent, (7.5% in vaccine recipients, 4.1% in placebo recipients), with the most prominent imbalance reported from South Africa (8.3% in vaccine group, 4% in placebo group).²² The reason behind this imbalance is still unclear. Of note, populations at higher risk of pre-term delivery (such as multiple births) were excluded from the trial and the rates of preterm delivery in the trial population were below the background rates raising concerns that the trial was underpowered to detect a significant increase in preterm births. However, 60% of preterm deliveries in the RSVpreF vaccine group occurred ≥ 30 days from vaccination and 5.5% occurred within 7 days of vaccination. As a result of these findings the FDA have advised administration at 32 through 36 weeks gestational age.²³ The EMA have indicated that administration of RSVpreF may occur between 24 and 36 weeks gestation.¹⁸

Figure 3. Serious Adverse Events in maternal and infant participants. Source: Kampmann et al.²⁰



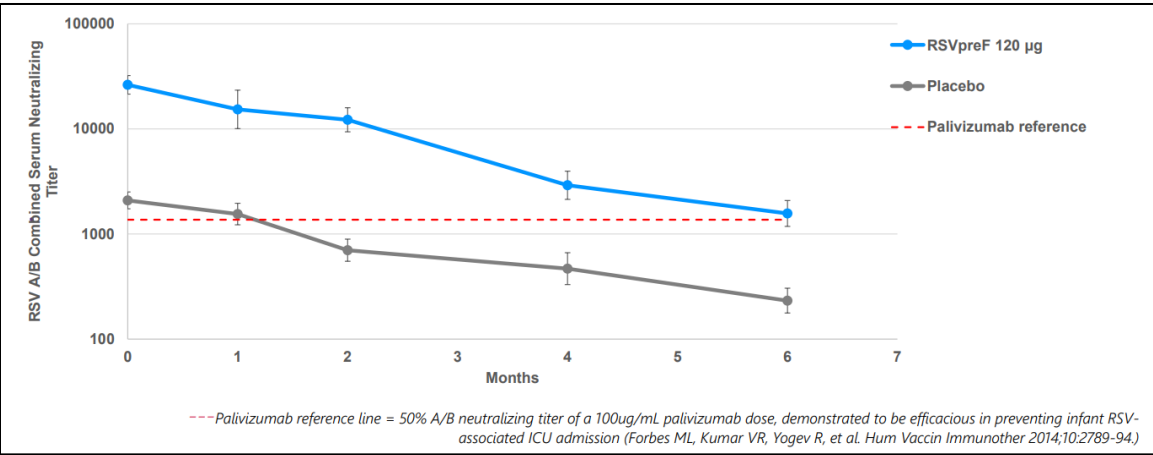
Serious adverse events in four vaccine recipients (pain in an arm followed by bilateral lower-extremity pain, premature labour, systemic lupus erythematosus, and eclampsia — in one recipient each) and one placebo recipient (premature placental separation) were assessed as being related to the injection. No serious adverse events in infants were considered to be related to the vaccine. A total of 17 deaths were reported in infants in the two-year follow up after birth, 5 in the vaccine group and 12 in the placebo group.²⁰

Immunogenicity

Immunogenicity data from the phase 2b SAVVY trial included just over 400 vaccine recipient (73 of which 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 recipient 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.²⁴

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.²⁵ (Figure 4)

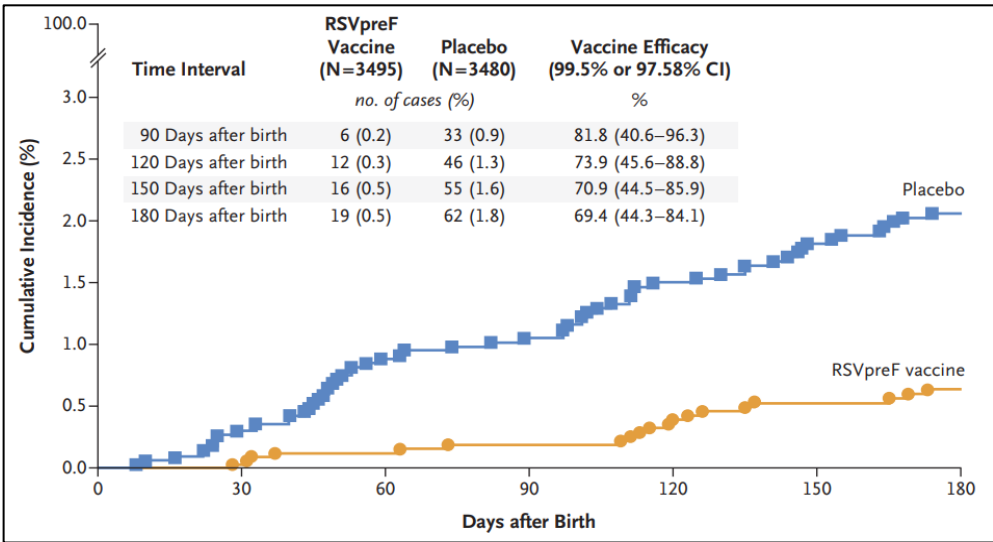
Figure 4. RSV A and B combined 50% geometric mean neutralising titres by month in infants born to mothers who received either vaccine or placebo at 24-36 weeks’ gestation. Source: ACIP CDC presentation.²⁵



Efficacy

Efficacy end points in the MATISSE study were medically attended RSV lower respiratory tract infection (LRTI) and medically attended severe RSV LRTI. Efficacy was greater against more severe disease and declined with time from birth. For medically attended RSV, vaccine efficacy was 57% at 90 days, declining to 51% by 180 days after birth. For severe medically attended RSV, vaccine efficacy was 82% at 90 days declining to 69% at 180 days after birth. (Figure 5) Hospitalisations due to RSV were reported as a secondary end point. Vaccine efficacy against hospitalisation was 68% at 90 days and 57% at 180 days after birth.²⁰

Figure 5. Medically attended severe RSV associated lower respiratory tract infection. Source: Kampmann et al.²⁰



Co-administration

Concomitant administration of Tetanus diphtheria and pertussis (Tdap), Influenza or COVID-19 vaccines with RSVpreF in pregnant individuals has not yet been studied. A Phase 2 placebo-controlled, randomized observer-blind study (NCT04071158) evaluated safety, tolerability, and immunogenicity of RSVpreF when administered concomitantly with Tdap in non-pregnant women 18-49 years of age.²⁶ There is no accepted correlate of protection for pertussis vaccination. In the absence of defined correlates of protection, non-inferiority is used to assess immunogenicity. Geometric mean antibody concentrations (GMCs) to the acellular pertussis antigens were lower in those who received Tdap concomitantly with RSVpreF, compared to those who received Tdap alone and did not meet prespecified non-inferiority criterion.²⁶ The clinical relevance of this finding is unknown and will need to be studied in post marketing surveillance. No safety or reactogenicity concerns were identified with coadministration of Tdap, influenza or COVID-19 vaccines in this trial. While coadministration with Tdap would likely increase feasibility, the EMA has recommended a minimum interval of two weeks between administration of RSVpreF and Tdap due to this concern regarding possible impact on Tdap immunogenicity. The EMA has however recommended that RSVpreF can be administered concomitantly with seasonal influenza vaccine.¹⁸

Nirsevimab; RSV long-acting monoclonal antibody

Nirsevimab (Beyfortus) is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.¹⁹

Nirsevimab was authorised in the EU based on data from three clinical trials;

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), 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).²⁷
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).²⁸
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).²⁹

In addition, since authorisation of nirsevimab preliminary data from the HARMONIE (Phase 3b) trial have been presented. HARMONIE assessed safety and efficacy in healthy infants born after

29 weeks' gestation randomised to receive either nirsevimab (n=4,016) or no intervention (n=4,020).³⁰

Safety

Nirsevimab has displayed an acceptable safety profile in all trials considered. The types and rates of adverse events were comparable between the treatment and placebo groups. The majority of adverse events reported were of mild to moderate severity.²⁷⁻³⁰ Adverse event of grade 3 or higher were reported more frequently in the placebo group than the nirsevimab group in both the MELODY and D5290C00003 trials.^{28 29}

In the MEDLEY trial the safety and side effect profiles were similar between those who received nirsevimab and those who received palivizumab, both in terms of frequency, severity and type of adverse events reported. No treatment related serious adverse events were reported in either group.²⁷

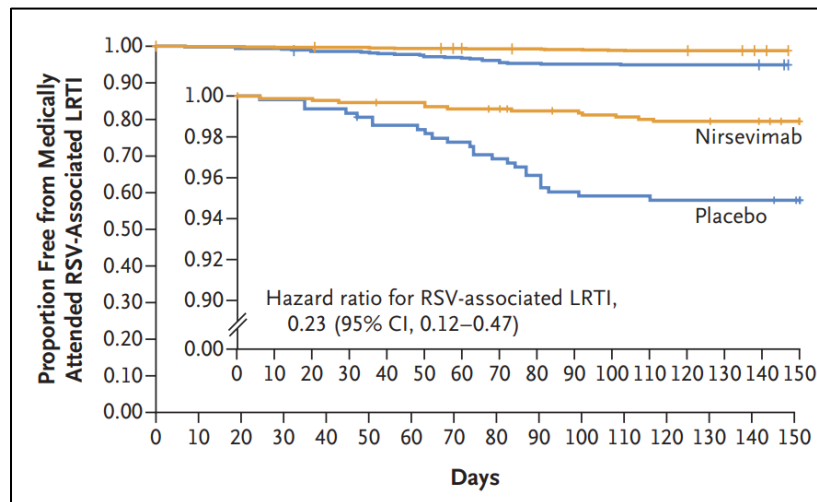
Immunogenicity and pharmacokinetics

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.^{27 29} Antidrug antibodies (ADAs) in all three trials were low, (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.²⁷⁻²⁹ 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

In the MELODY trial, southern hemisphere participants contributed no events to the primary efficacy estimate due to a non-existent RSV season in the winter of 2020 secondary to the COVID-19 pandemic. Hence, all efficacy data was collected from the northern hemisphere and was somewhat limited. The primary end point was medically attended RSV associated LRTI which occurred in 1.2% of the nirsevimab group compared to 5% of the placebo group, resulting in a 75% efficacy. (Figure 6) Through 150 days post-dose, 0.6% of the nirsevimab group and 1.6% of the placebo group were hospitalised with RSV LRTI, resulting in an efficacy estimate of 62% against hospitalisation.²⁹

Figure 6. Proportion of participants free from medically attended RSV associated LRTI in term and late preterm infants. Source: Hammitt et al.²⁹



In the D5290C00003 trial which was carried out in winter 2016/2017 medically attended RSV was 70% lower in the nirsevimab group (9.5%) compared to the placebo group (2.6%) ($p<0.001$) and hospitalised RSV was 78% lower in the nirsevimab group (0.8%) compared to the placebo group (4.1%) ($p<0.001$) through 150 days post-dose. Also of note, all patients admitted to ICU ($n=5$) or requiring assisted ventilation ($n=4$) were in the placebo group.²⁸

The HARMONIE trial reported that 0.3% of the nirsevimab group were hospitalised with RSV LRTI compared to 1.5% of the non-intervention group, resulting in an efficacy of 83% against hospitalisation ($p<0.0001$). In addition, an efficacy of 76% was reported against severe RSV disease causing hospitalisation and an efficacy of 58% was reported for all cause LRTI related hospitalisation through the first RSV season.³⁰

Coadministration

Since nirsevimab is a monoclonal antibody specific for RSV, it would not be expected to interfere with the active immune response to co-administered vaccines. The MEDLEY and the MELODY trials both recorded safety and reactogenicity of childhood vaccines when co-administered with nirsevimab. In the MELODY trial similar rates of vaccine related side effects occurred in both groups (26/987(2.6%) vs 15/491 (3.1%)). Similarly in the MELEDY trial there were no differences in rates of vaccine related side effects reported in nirsevimab and palivizumab recipients. The EMA has thus approved concomitant administration of nirsevimab with childhood vaccines.¹⁹

Implementation considerations (Table 2)

Timing of immunisation

The optimal timing of nirsevimab administration to obtain maximum benefit is just prior to the onset of the RSV season considering the duration of its protective effects, and the seasonal nature of RSV. This would likely require administration at birth, or very soon after to those born during the RSV season, and administration at the commencement of the RSV season (early autumn) to those aged less than eight months of age. In the United States the CDC has advised administration at routine two, four or six month immunisation visits occurring between September and November. Spain and France are the only European countries to announce plans to administer nirsevimab for the 2023/24 RSV season. The Spanish campaign will start in October in most regions, with a plan to immunise all infants born during the RSV season at, or soon after birth, and those born out of season aged less than six months of age are to be immunised in the month of October.³¹ In France infants born from 15 Sept 2023 to end of January 2024 will be vaccinated prior to discharge from maternity hospitals. Those born from 6 Feb 2023 to 15 Sept 2023 will be immunised at the start of the RSV season.³²

It may be challenging to accurately predict the start of the RSV season, especially in the context of recent shifts, in which the RSV seasons in 2021 and 2022 started earlier than previous years. An alternative strategy proposed for consideration by the UK is to administer nirsevimab to all infants at birth year-round in order to simplify implementation.³³ However, this would likely offer limited benefit to those who receive a dose in spring or early summer. Real world experience from countries using nirsevimab this season will help guide implementation strategy for future seasons.

In the MATISSE trial, the maternal RSV vaccine was administered within a three-month period, 24-36 weeks' gestation. Notably, the timing of administration within this window did not demonstrate an impact on infants' antibody levels. This could facilitate administration at any antenatal visit during this period, potentially improving uptake. To date the US is the only jurisdiction to have made a formal recommendation regarding maternal RSV vaccination. To mitigate against any potential risk of preterm delivery they have recommended maternal RSV vaccination to pregnant people between 32- and 36-weeks gestation. They have also recommended a seasonal approach, whereby vaccination should only be offered to those due to deliver during the RSV season. This was based on economic analysis which determined that because protection for infants does not extend beyond six months of age, the most valuable strategy for maternal vaccination was to restrict maternal vaccine to the months of the year when infants would benefit from immediate protection during the RSV season. Of note, they recommend nirsevimab for infants younger than 8 months of age who were born shortly before or are entering their first RSV season in the following scenarios; 1) the mother did not receive the RSV vaccine during pregnancy, 2) infants born within two weeks of maternal vaccine receipt; or 3) maternal vaccination status is unknown.^{34 35}

As most placental antibody transfer occurs in the third trimester, infants born prematurely are unlikely to gain adequate maternal antibody prior to birth following maternal RSV vaccination. Hence, monoclonal antibody administration would still need to be available to this cohort of preterm neonates, especially in the context of their higher baseline risk of severe RSV related disease. Additionally, if a maternal vaccination strategy were to be adopted, term infants at high-risk of severe RSV disease (such as those with haemodynamically significant CHD) whose mothers do not receive the vaccine, due to personal choice or other reasons, would need to receive monoclonal antibody. Infants born within two weeks of maternal vaccination are also less likely to have acquired adequate maternal antibody and could benefit from monoclonal antibody administration.

Table 2. Implementation considerations for passive immunisation of infants against RSV.

Population	Administration
Infant nirsevimab administration	
Infants born during RSV season ^a	Administer nirsevimab soon after birth, ideally prior to discharge from maternity hospital ^b
Infants born outside of RSV season ^a	Administration of nirsevimab with 2, 4 or 6 month vaccines between Aug and Oct ^a
High-risk ^c infants and children	Nirsevimab to be administered between September and October
Maternal RSV vaccination	
Pregnant women	Year-round or seasonal administration of RSV vaccine once in pregnancy between 24- and 36-weeks' gestation
High-risk ^c infants	Nirsevimab to be administered between September and October. If nirsevimab not available for palivizumab administration as per current guidelines. ¹⁵
Additional considerations	Infants born less than two weeks after maternal vaccination should receive a dose of nirsevimab as per administration guidance above depending on their season of birth. For those who do not receive maternal RSV vaccine in pregnancy, nirsevimab administration may be considered.
^a The estimated timing of the RSV season will need to be reviewed on an annual basis ^b For those who cannot have nirsevimab administered prior to discharge; arrange administration as soon as is feasible. ^c High risk infants defined as those eligible for palivizumab administration in Chapter 18a of the National Immunisation Guidelines ¹⁵	

Acceptability

The acceptability of antenatal vaccination and neonatal monoclonal antibody use should be considered carefully as it has a significant impact on uptake rates. Historically, achieving good uptake of antenatal vaccines in Ireland and internationally has been challenging. If an RSV maternal vaccine is to be introduced, it is important to reflect on the factors that have previously contributed to successful antenatal vaccine uptake and work towards minimising barriers to vaccination.

Reporting an accurate estimate of vaccine uptake in pregnancy in Ireland is challenging as this is not routinely monitored. Population-based sampling from 2017-2018 estimated influenza vaccine uptake to be 61.7% (95% CI: 55.3-67.8) and pertussis uptake to be 49.9% (95% CI: 43.3–56.6).³⁶ More recent single centre surveys suggest that uptake may be improving, especially for pertussis vaccine, however, these are limited by a selection bias that likely over-estimates vaccine uptake.³⁷ Determining current pertussis vaccine uptake rates during pregnancy in Ireland would be useful in predicting maternal RSV vaccine uptake, as the primary goal of both these vaccines is infant benefit.

Concerns regarding the safety of antenatal vaccines has been reported to be one of the most important deterrents to pregnant women coming forward for vaccination.³⁸ This is particularly true for novel vaccines. Ensuring pregnant women and their healthcare providers are well informed regarding vaccine safety is crucial.

Strong health care provider recommendations are one of the most important facilitators of vaccine uptake in pregnancy.³⁹ The effectiveness of such recommendations is tied to the level of confidence healthcare workers have in the vaccines and their knowledge of the underlying safety and efficacy data. In Ireland, several studies have demonstrated a variability in knowledge and confidence in maternal vaccines among obstetricians, midwives and general practitioners.^{40 41}

In Ireland, maternal vaccines, for the most part, are delivered in primary care. Accessibility of vaccines has been shown to impact maternal uptake. Research in the United States and the UK demonstrates that making vaccines available in antenatal clinics can increase uptake.⁴²⁻⁴⁴ A recent pilot study in a single antenatal clinic (DOVE clinic) at the Rotunda Hospital reported that when offered vaccines at antenatal visits, only 8% refused pertussis vaccination.⁴⁵

Infant vaccination uptake rates are usually above 85% in the first year of life, albeit Ireland has seen some decline in recent years.⁴⁶ Nonetheless, the concept of universally administering a monoclonal antibody as part of an immunisation programme is unprecedented. This novel approach may elicit some hesitancy in parents reluctant for their infants to receive a new product. A study funded by the manufacturer of nirsevimab reported good acceptability of monoclonal antibodies in theory, however there is a paucity of independent research.⁴⁷ Further research into the acceptability of monoclonal antibodies to parents would be useful in trying to estimate the uptake.

Awareness of RSV and the severity of the disease in infants is an important consideration for both parents and pregnant women in considering the need for immunisation. In advance of either product being introduced, it would be important to understand the extent of knowledge about RSV in the community, and to promote a good understanding of the impact of RSV targeting both parents and healthcare providers.

5. RSV IMMUNISATIONS FOR OLDER ADULTS

Two recombinant RSV vaccines have been developed and approved for the prevention of lower respiratory tract disease (LRTD) in individuals 60 years of age 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).^{18 48}

RSVPreF3 (Arexvy, GSK)

RSVPreF3 (Arexvy, GSK) is a one dose (0.5 mL) adjuvanted (AS01E) recombinant stabilised prefusion F protein (preF) vaccine.

Safety

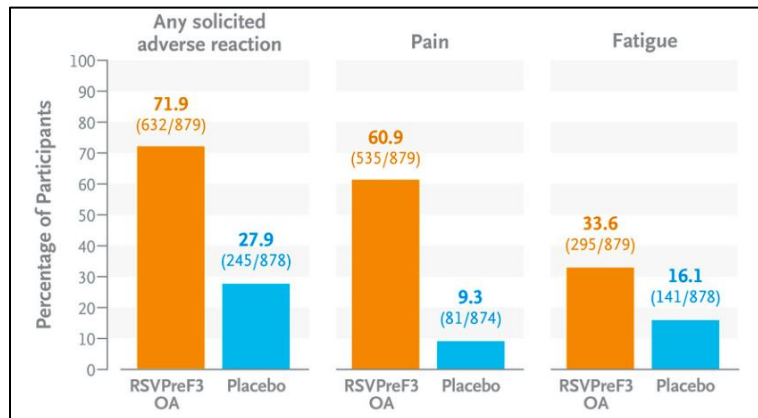
Evidence regarding safety of RSVPreF3 includes data from two randomised, double-blind, placebo-controlled clinical trials, including an ongoing phase 3 trial and a phase 1/2 trial in adults aged ≥ 60 years who received either the vaccine formulation used in the phase 3 trial or placebo (n=24,966 and n=201 respectively).^{49 50}

The RSVPreF3 vaccine was generally well tolerated with an acceptable safety profile.

The vaccine was more reactogenic than placebo. Across both clinical trials, severe reactogenicity events occurred in 3.8% of the intervention group participants, compared with 0.9% of the control group participants (pooled relative risk [RR] = 4.10; 95% CI = 1.99-8.45).

Most adverse events for which reports were solicited were transient, with mild-to-moderate severity. The most common side effects reported in those who received the vaccine were injection site pain and fatigue. (Figure 7)

Figure 7. Safety outcomes in recipients of RSVPreF3 compared to placebo. Source: Papi et al.⁴⁹



The frequency of serious adverse events (SAEs) across both trials was similar in the intervention (4.4%) and control (4.3%) groups (pooled RR = 1.02; 95% CI = 0.91-1.15).

A higher number of participants in the intervention group than in the control group reported atrial fibrillation as an unsolicited event within the 30 days after injection (intervention = 10 events [0.1%]; control = four events [<0.1%]), eight of which were SAEs [intervention = seven; control = one]; three of the SAEs corresponded to new onset atrial fibrillation (intervention = two; control = one). Of note, at six months post vaccination the incidence of atrial fibrillation was similar in both groups (intervention = 14, placebo = 16).⁵¹

Across all RSVPreF3 vaccine clinical trials in older adults, inflammatory neurologic events were reported in three of 17,922 participants within 42 days after receipt of the RSVPreF3 vaccine. All three events occurred in trials excluded from GRADE because of lack of an unvaccinated comparator arm. The reported cases included one case of Guillain-Barré syndrome (GBS) and two cases of acute disseminated encephalomyelitis (ADEM) among participants in a randomised phase 3 coadministration study.

Immunogenicity

In a per-protocol immunogenicity cohort including 1,702 participants between baseline and one month after RSVPreF3 vaccine, the concentrations or titres for RSVpreF3-specific IgG antibodies increased by a factor of 13.1, by a factor of 10.2 for RSV A neutralizing antibodies, and by a factor of 8.6 for RSV B neutralizing antibodies.⁴⁹

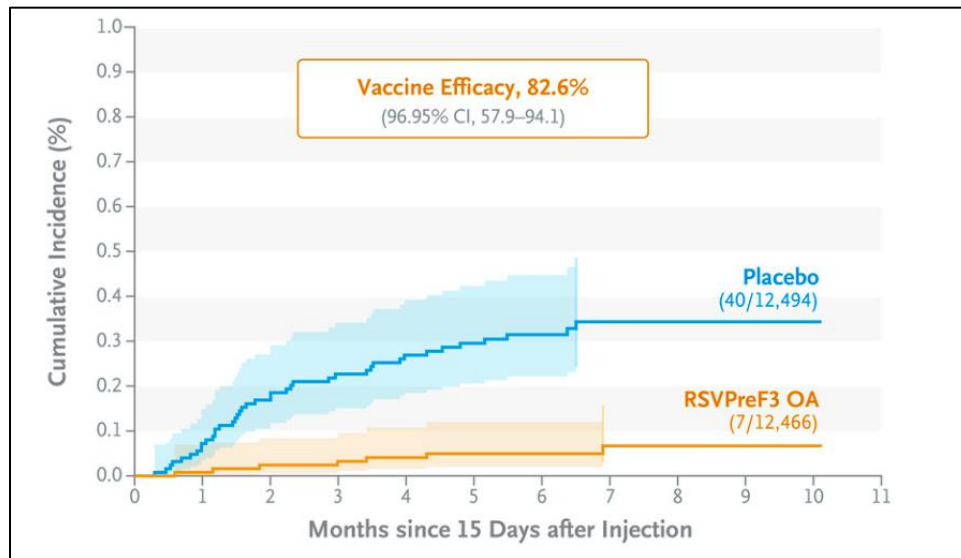
Efficacy

Vaccine efficacy data are available from one large phase 3 randomised, double-blind, placebo-controlled clinical trial including 24,973 immunocompetent participants aged 60 years and older.⁴⁹ In this trial, a single dose of RSVPreF3 reduced symptomatic RSV LRTD by 82.6% (96.95% CI =

57.9%-94.1%) during the first RSV season, and by 56.1% (95% CI = 28.2%-74.4%) during the second RSV season. (Figure 8)

Figure 8: Vaccine efficacy of RSVPreF3 against RSV-Related Lower Respiratory Tract Disease.

Source Papi et al.⁴⁹



Efficacy of one dose of RSVPreF3 over two seasons was 74.5% (97.5% CI = 60.0%-84.5%) in preventing RSV-associated LRTD, and 77.5% (95% CI = 57.9%-89.0%) in preventing medically attended RSV-associated LRTD.⁵²

The trial was underpowered to demonstrate efficacy against RSV-associated hospitalisation (intervention group = one event; control group = five events), severe RSV illness requiring respiratory support (intervention group = one event; control group = five events), or death (no events).

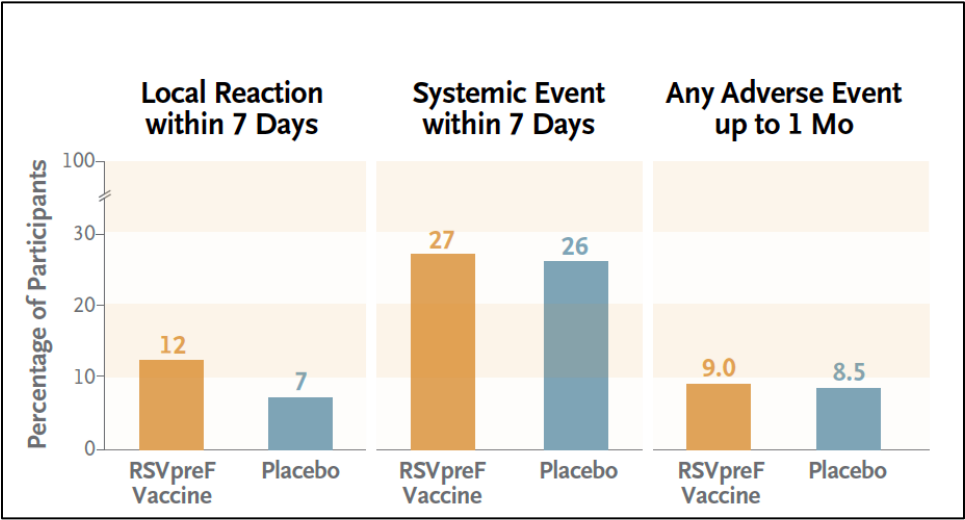
RSVpreF (Abrysvo, Pfizer)

RSVpreF (Abrysvo, Pfizer) is a one dose (0.5 mL) recombinant stabilized preF vaccine.

Safety

In clinical trials among adults aged 60 years and older, vaccine-related reactions were common among participants who received the RSVpreF vaccine. The most common reactions in the large phase 3 clinical trial were fatigue (16%), headache (13%), and pain at the injection site (11%). Grade 3 reactions (severe enough to prevent normal daily activities) occurred in approximately 1% of vaccine recipients.⁵³ (Figure 9)

Figure 9. Adverse events in recipients of RSVpreF compared to placebo. Source: Walsh et al.⁵³



Across all clinical trials in adults aged 60 years and older, inflammatory neurologic events were reported in three of 20,255 participants within 42 days after receipt of the RSVpreF vaccine. The events included one case of GBS with symptom onset 14 days postvaccination, one case of Miller Fisher syndrome (a GBS variant) with symptom onset 10 days postvaccination; and one case of undifferentiated motor-sensory axonal polyneuropathy with worsening of pre-existing symptoms 21 days postvaccination.⁵²

In the large phase 3 clinical trial, a higher number of participants who received RSVpreF vaccine than those who received placebo reported atrial fibrillation within the 30 days after injection (10 vs. 4 participants).⁵²

Immunogenicity

Immunogenicity was assessed in a phase 1/2 study of 317 adults aged 65-85, 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 60mcg, 120 mcg and 240mcg. 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.⁵⁴

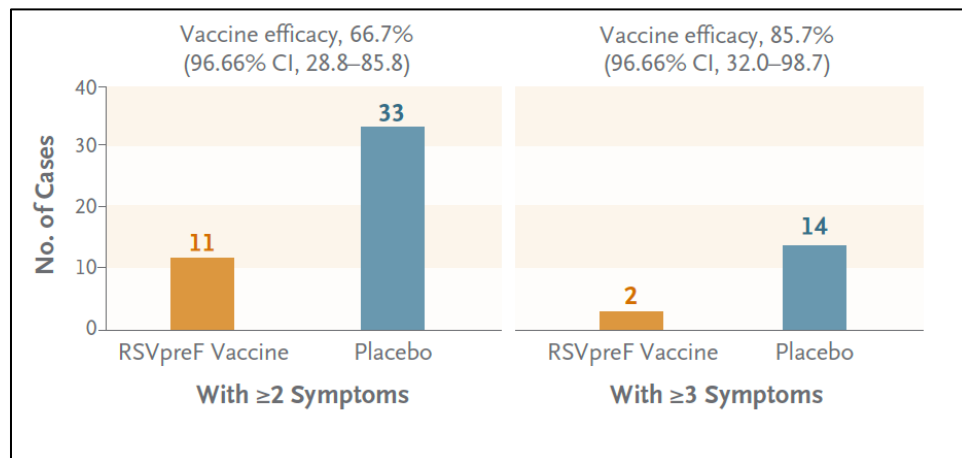
Efficacy

Vaccine efficacy data are available from one large phase 3 randomized, blinded, placebo-controlled clinical trial which included 36,862 immunocompetent participants aged 60 years and older, randomized 1:1 to receive one dose of vaccine (intervention group, 120 µg preF protein) or placebo containing the same buffer ingredients as the vaccine but without active components (control group).⁵³

In this trial, a single dose of the RSVpreF reduced RSV LRTD with 3 or more lower respiratory signs and symptoms by 88.9% (95% CI = 53.6%-98.7%) during the first RSV season after vaccination compared to a placebo, and by 78.6% (95% CI = 23.2%-96.1%) during a partial second RSV season (interim estimate; the second season efficacy will be updated upon study completion).

Efficacy of a single dose over two seasons was 84.4% (95% CI = 59.6%-95.2%) in preventing RSV-associated LRTD and 81.0% (95% CI = 43.5%-95.2%) in preventing medically attended RSV-associated LRTD. (Figure 10)

Figure 10. Vaccine efficacy of RSVpreF against RSV associated lower respiratory tract illness. Source: Walsh et al.⁵³



The trial was underpowered to demonstrate efficacy against RSV-associated hospitalisation (intervention group = one event; control group = three events) severe RSV illness requiring respiratory support (intervention group = one event; control group = one event), or death (no events).

Coadministration

Coadministration of RSV vaccines with influenza vaccines during the same visit is thought to be acceptable. Coadministration of RSV and seasonal influenza vaccines met noninferiority criteria for immunogenicity with the exception of the FluA/Darwin H3N2 strain when the RSVPreF3 was

coadministered with adjuvanted quadrivalent inactivated influenza vaccine. RSV and influenza antibody titres were numerically lower with coadministration; however, the clinical significance of this is unknown.^{51 54}

Administering RSV vaccine with one or more other vaccines at the same visit may increase local or systemic reactogenicity. Data are only available for coadministration of RSV and influenza vaccines.

Available data on safety and immunogenicity of coadministration of RSV vaccines and other vaccines are currently limited. Post licensure efficacy and safety monitoring of RSV vaccines co-administered with other vaccines will further direct future guidance.

Implementation Considerations

Timing of immunisation

RSV vaccination of adults 65 years and older should ideally occur before the onset of the autumn/winter RSV season. However, typical RSV seasonality was disrupted by the COVID-19 pandemic with early emergence of RSV cases in 2021/2022. Enhanced epidemiological surveillance may help inform optimal timing of an RSV vaccination campaign for older adults.

RSV vaccines appear to provide some protection for at least two RSV seasons in older adults. Future research and real-world data will provide further information regarding how long the vaccines protect against RSV and whether additional doses will be needed.

Acceptability

RSV is well-recognised as a significant health issue in infants however there is lower awareness of the health impacts of RSV for older adults in both healthcare providers and the public. There is limited available data regarding acceptability of RSV vaccine in older adults. A survey, developed by CDC in collaboration with the University of Iowa and the RAND corporation to assess vaccination intentions for a hypothetical RSV vaccine among U.S. adults aged 60 years and older found that 68% of respondents said they 'definitely' or 'probably' would choose to get vaccinated if a safe and effective FDA-approved RSV vaccine was available. Additionally, 77% said they 'definitely' or 'probably' would get an RSV vaccine if it were recommended by a healthcare provider.⁵⁵

In Ireland, uptake of recommended vaccines in older adults is high including seasonal influenza vaccine and COVID-19 vaccine. It is likely that uptake of RSV vaccine as part of an autumn/ winter vaccine programme would be similarly high once benefit risk of vaccine was communicated and recommendation made by a healthcare provider.

6. INTERNATIONAL POSITIONS

Table 3. International recommendations regarding RSV immunisation as of 9 October 2023.

Country	Infants and children	Older adults
Austria ⁵⁶	No recommendation to date	<ul style="list-style-type: none"> RSV vaccination (RSVpreF or RSVPreF3) is recommended to adults aged over 60 years of age. It may also be considered in those aged 18-60 years with underlying conditions associated with increased risk of severe disease.
Belgium ⁵⁷	No recommendation to date	RSV vaccination is recommended on an individual basis for adults aged 60 and above with at least one risk factor for severe disease.
France ³²	<p>Recommendation for nirsevimab to be given to</p> <ul style="list-style-type: none"> infants prior to discharge from maternity hospital from 15 Sept 23 to end of Jan 2024. infants born since 6 Feb 2023 at start of RSV season. Infants and children in whom palivizumab is recommended. <p>Assessment of maternal vaccine underway</p>	Assessment underway, decision due Oct 2024
Spain ^{58 59}	<p>Recommendation for nirsevimab to be given to</p> <ul style="list-style-type: none"> all infants aged less than 6 months in children aged less than 2 years of age with underlying diseases that increase the risk of severe RSV infection. <p>Galacia region are first to announce implementation plan, most other Spanish regions expected to implement for the 2023/2024 season</p>	No recommendation to date
Sweden ⁶⁰	No recommendation to date	<p>RSV vaccination recommended for;</p> <ul style="list-style-type: none"> all those aged 75 years and older recommended Those aged 60 and older with medical conditions which may increase risk of severe disease.

Norway ⁶¹	No recommendation to date	The RSV vaccine (RSVPreF3) may be considered for adults aged 60 years and older with underlying disease.
UK ⁶²	<p>Universal RSV infant programme advised by JCVI with no product preference (nirsevimab or maternal vaccination)</p> <p>No implementation plan to date</p>	<p>RSV vaccination of those aged 75 years and above advised by JCVI with no product preference (considered RSVPreF3, RSVpreF, and mRNA-1345)</p> <p>No implementation plan to date</p>
USA ^{34 35 63-66}	<p>One dose of nirsevimab is recommended for infants younger than 8 months of age who were born shortly before or are entering their first RSV season if;</p> <ul style="list-style-type: none"> • The mother did not receive RSV vaccine during pregnancy. • The mother's RSV vaccination status is unknown. • The infant was born within 14 days of maternal RSV vaccination <p>For high risk infants aged 8-19 months, a dose is also recommended for their second RSV season.</p> <p>Recommendation for maternal RSV vaccine (RESpreF);</p> <ul style="list-style-type: none"> • Recommended for pregnant people during 32 through 36 weeks gestation, using seasonal administration targeting infants due to be delivered during the RSV season. • Those due for delivery outside of the RSV season are not recommended to receive a maternal RSV vaccine, instead their infants are recommended for nirsevimab as outlined above. • Certain high-risk infants are also recommended to receive nirsevimab regardless of maternal immunisation status • Those born within two weeks of maternal RSV vaccination are also recommended to receive nirsevimab. 	<p>RSV vaccination (either RSVPreF3 or RSVpreF) recommended to those aged 60 years and older with shared clinical decision making</p>

7. CONCLUSION

RSV causes a significant burden of disease in both infants and older adults in Ireland, placing considerable strain on the healthcare system particularly in the winter months. There are now two EU authorised vaccines and a long-acting monoclonal antibody that could dramatically reduce this burden. Two recombinant RSV vaccines, with similar efficacy and safety profiles have been developed and approved for the prevention of lower respiratory tract disease in individuals 60 years of age and older. A maternal vaccine and an infant long-acting monoclonal antibody with similar efficacy and safety profiles have been approved for the protection of infants. Careful consideration of additional factors, including acceptability, delivery, and cost will be important in determining the most effective strategy for infants.

Robust surveillance systems to measure the impact of a RSV immunisation programme and to aid prediction of the onset of the RSV season will be important moving forward, both for guiding policy and measuring the impact of an RSV immunisation program. Of particular interest would be to ascertain data during the 2023/2024 RSV season on the profile of children aged over one year of age, and adults hospitalised with RSV regarding demographics, background co-morbidities, and outcomes, as this could inform decisions regarding vaccination of higher risk groups in the future.

The success of any immunisation programme will depend on uptake in the target population. Thus, regardless of the chosen strategy, systems should be put in place to measure vaccine uptake in each of the different target populations. It is timely to reflect on the challenges in obtaining accurate statistics on maternal vaccine uptake in Ireland. Should a maternal vaccine strategy be proposed, it would be critical that vaccine uptake in pregnancy could be accurately measured. Collecting data on knowledge and awareness of RSV, and attitudes towards candidate vaccines and nirsevimab will help inform public health messaging.

Current evidence clearly supports the passive immunisation of infants against RSV during their first RSV season. Given the burden placed by RSV on the Irish healthcare system, efforts should be made to implement a programme for infants and older adults as soon as is feasible. Determining policy and planning an effective implementation strategy will take time and requires engagement from multiple stakeholders. There are several more RSV immunisation products in the final stages of clinical development. NIAC will continue to review RSV epidemiology and new scientific data on an ongoing basis, and provide updated guidance where appropriate.

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