Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Rapid health technology assessment of immunisation against respiratory syncytial virus (RSV) in Ireland

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory body established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector of Social Services within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services** — Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of permanent international protection accommodation service centres, health services and children's social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children's social services.

- **Health technology assessment** — Evaluating the clinical and cost effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health and social care services, with the Department of Health and the HSE.

Foreword

Respiratory syncytical virus (RSV) is a highly contagious respiratory virus. In healthy individuals, infection with RSV is usually self-limiting. However, RSV can cause more severe infections, such as pneumonia and bronchiolitis, which may lead to hospitalisation and death. Those at increased risk of severe infection include infants aged under six months, premature infants, children aged under two years with congenital heart or lung disease, and older adults, particularly those with comorbidities or who are immunocompromised.

Protection against RSV is not currently offered to healthy infants and adults in Ireland. However, palivizumab (Synagis®) is provided by the Health Service Executive (HSE) for specified paediatric populations who are considered at high risk of severe disease caused by RSV. Recently, two additional forms of immunisation for infants have been authorised in Europe. The first, nirsevimab (Beyfortus®), is administered directly to the infant, and the second, RSVpreF (Abrysvo®), is administered to pregnant women, thus providing infant protection through transplacental antibody transfer. Two vaccines have also been authorised for the immunisation of adults aged 60 years and older: RSVpreF (Abrysvo®) and RSVPreF3 (Arexvy®).

On 18 June 2024, the Minister for Health announced the temporary RSV Immunisation Pathfinder Programme which is being piloted for the 2024-2025 season. Through this programme, parents of babies born from September 2024 to February 2025 will be encouraged to have their babies immunised with nirsevimab before leaving the maternity unit. The purpose of this rapid health technology assessment (HTA) is to provide advice to inform a policy decision on immunisation against RSV (in children and older adults) in Ireland for the 2025-2026 season.

This rapid HTA was undertaken by an Evaluation Team from the HTA Directorate at HIQA. A multidisciplinary Expert Advisory Group (EAG) was convened to advise the Evaluation Team during the course of the rapid HTA. HIQA would like to thank the Evaluation Team, the members of the EAG and all who contributed to the preparation of this draft report.

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Deputy Chief Executive & Director of Health Technology Assessment

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Table of contents

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Organisations that assisted HIQA in providing information, in writing or through meetings, included:

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Healthcare Pricing Office, HSE

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Members of the Evaluation Team:

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Conflicts of Interest

There were no reported potential conflicts of interest for the EAG or members of the Evaluation Team. It is noted that general practitioners may derive a small portion of their income from the administration of vaccines.

Key Findings and Advice to the Minister for Health and Health Service Executive

At the request of the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a rapid health technology assessment (HTA) of alternative infant and adult immunisation strategies against RSV in Ireland. The rapid HTA was submitted as advice to the Minister for Health and Health Service Executive (HSE) to inform an interim policy decision on the most appropriate RSV immunisation strategy for the 2025-2026 season. This advice was provided in the context of clinical recommendations from the National Immunisation Advisory Committee (NIAC) to the Department of Health.

The key findings of this rapid HTA, which informed HIQA's advice to the Minister for Health and HSE, were:

- Respiratory syncytial virus (RSV) is a highly contagious ribonucleic acid (RNA) virus, which is transmitted through airborne respiratory droplets via coughing, sneezing or breathing. Primary infection with RSV can cause lower respiratory tract disease (LRTD) in infected individuals. RSV has been a notifiable disease in Ireland since 2012.
- In Ireland, RSV outbreaks typically occur in the winter months, with the highest number of infections usually reported in December and January, although RSV activity can peak earlier.
- In healthy individuals, infection with RSV is usually self-limiting, and can be managed without medical attendance. However, RSV can cause more severe infections, such as pneumonia and bronchiolitis, which can lead to hospitalisation and can be fatal. RSV may also exacerbate chronic health conditions, in particular respiratory and circulatory conditions.
    - Children at highest risk of serious LRTD caused by RSV include infants aged under six months, premature infants, children aged under two years with congenital heart or lung disease, children who are immunocompromised, and children with respiratory or neuromuscular disorders.
    - Adults at highest risk of severe RSV include older adults (that is, those aged 65 years and older), particularly those with comorbidities (such as chronic heart and lung disease), and those who are immunocompromised.

- Strategies for prevention of RSV in the general population typically focus on encouraging behaviours which may reduce virus transmission, such as reducing social contacts when an individual is symptomatic, and encouraging good hand hygiene and respiratory hygiene practices.

- A number of forms of immunoprophylaxis are authorised in Europe that provide passive immunisation against RSV in children; since 2022, these now include options for infants in the general population.

    - The monoclonal antibody, palivizumab (Synagis®), has been authorised in Europe since 1999. It is indicated for specified infant populations considered at high risk of serious complications of LRTD caused by RSV, and is administered by intramuscular injection at monthly intervals during the RSV season (typically up to five doses).

    - In October 2022, a long-acting monoclonal antibody, nirsevimab (Beyfortus®) was authorised and is administered by intramuscular injection, with a single dose sufficient to infer protection against RSV for that season.

    - In August 2023, a recombinant bivalent vaccine RSVpreF (Abrysvo®) was authorised for use in pregnant women, to provide passive immunisation of infants from birth to six months of age through transplacental antibody transfer.

- Since June 2023, two vaccines have been authorised in Europe for the immunisation of adults aged 60 years and older for prevention of LRTD caused by RSV: the recombinant bivalent vaccine RSVpreF (Abrysvo®), and the recombinant adjuvanted vaccine RSVPreF3 (Arexvy®).

- Nirsevimab, RSVpreF and RSVPreF3 are all subject to additional monitoring requirements by the European Medicines Agency, owing to the fact that they contain new active substances, and are new biological medicines.

- In Ireland, immunisation against RSV is recommended by the National Immunisation Advisory Committee (NIAC) for all infants in their first RSV season and for adults aged 65 years or older. Palivizumab is currently funded by the HSE for infants and children at highest risk of severe LRTD caused by RSV; NIAC has recommended that nirsevimab replaces palivizumab for this cohort. A publicly-funded pilot is being implemented that offers immunisation with nirsevimab to all infants born during the 2024-2025 RSV season. For older adults, currently no RSV immunisation programme is in place, or planned, for the 2024-2025 RSV season.

- A review of international practice was undertaken to identify recommendations and policy decisions with respect to the immunisation of infants and older adults against RSV in EU/EEA countries and the UK, with data identified for 31 countries including Ireland. Given the recency of authorisation of nirsevimab and the RSV vaccines, it is noted that international practice is changing rapidly. Considering the other EU/EEA countries and the UK, as of 1 July 2024:
    - Five countries (Belgium, France, Germany, Spain and the UK) have announced publicly-funded (or partially funded) immunisation programmes for the 2024-2025 RSV season. All five will offer immunisation to all infants entering their first RSV season, irrespective of whether they were born during or outside of the RSV season. However, the programmes vary in terms of the method of immunisation (that is, use of nirsevimab and or the maternal vaccine), eligibility (in terms of the gestational window for the maternal vaccine), the periods during which immunisation can be accessed (defined period or year-round), and priority groups for immunisation (for example, in the event of limited supply).
    - One country (the UK) has announced public funding of RSV vaccination for older adults (once-off for all adults aged 75 to 79 years which will be implemented from September 2024), while in the Czech Republic, RSV vaccines are available on an individual basis for adults aged 60 years or older and are partially funded through insurance.
    - For the five countries with publicly-funded programmes, two (Belgium and Spain) have specified that their outlined approach to immunisation is for the 2024-2025 RSV season only, and will be reviewed for subsequent seasons. The others have highlighted that the programmes may be updated in line with the latest evidence.
- National recommendations in the countries examined were informed by the national and international epidemiology and burden of RSV and the rapidly evolving evidence in relation to each form of immunisation.
    - For nirsevimab, recommendations have been informed by evidence of efficacy and safety from five randomised controlled trials (RCTs) in addition to preliminary surveillance data from countries that implemented a programme of immunisation with nirsevimab during the 2023-2024 RSV season (namely Spain, Luxembourg and the US).
    - For the maternal vaccine, countries that have conducted assessments have primarily considered evidence from one RCT (MATISSE).

  - National recommendations on RSV vaccination for older adults were primarily informed by the results of five RCTs: two related to RSVPreF3 (Arexvy®) and three related to RSVpreF (Abrysvo®). Further data provided by manufacturers informed recommendations in the US, which in turn informed recommendations in both Ireland and Sweden.

  - Published trial data for nirsevimab, the maternal vaccine and RSV vaccines for older adults that supported recommendations in the countries included in the review suggest that these agents are safe and effective. Moreover, early evidence of real-world safety and effectiveness of nirsevimab from countries that implemented immunisation for infants in the 2023-2024 season is broadly consistent with these trial data.

- Health Protection Surveillance Centre (HPSC) data indicate that, between 2013 and 2023, the annual burden associated with RSV varied. However, in all years, the highest burden in terms of notified RSV cases, and RSV-associated emergency department (ED) visits and hospitalisations was consistently in children aged 0 to 4 years. For example, annual rates of RSV-related hospital admissions per 100,000 ranged from 190.3 to 790.1 in children aged 0 to 4 years compared with 1.3 to 74.6 in adults aged 65 years and older.

- The HPSC data also indicate that among:

  - those aged 0 to 4 years, approximately two-thirds of notified cases, RSV-related ED attendances and hospital admissions occurred in infants aged less than one year, with a disproportionate number of admissions occurring in those aged less than six months.

  - adults aged 65 years and older, burden typically increased with age, with on average almost half of notified cases, RSV-related ED attendances and hospital admissions reported in adults aged 80 years and older.

- Hospital utilisation data for those aged 0 to 4 years and those aged 65 years and older were sourced from the Hospital In-Patient Enquiry (HIPE) system for 2013 to 2022. These data showed that there is a substantial burden associated with RSV in terms of hospitalisations and ICU admissions. While the annual burden has varied, the highest burden was consistently seen in those aged 0 to 4 years, with the majority of this burden seen in those aged less than one year, and occurring in quarter four (October to December) each year. Annual mortality rates were consistently low in all age groups. In those with a primary diagnosis of RSV, on average, each year:

- there were 1,341 (range: 790 to 2,259) discharges that did not include an intensive care unit (ICU) stay in children aged 0 to 4 years (infants aged less than one year accounted for 84% of these discharges) compared with a total of 225 discharges between 2013 and 2023 in adults aged 65 years and older.

- there were 121 (range: 62 to 201) discharges that included an ICU stay in children aged 0 to 4 years (infants aged less than one year accounted for 90% of these discharges) compared with typically fewer than five such discharges a year in those aged 65 years and older.

- for children aged 0 to 4 years, hospital discharges in the fourth quarter accounted for the greatest proportion of annual discharges, ranging from 71% to 91% (of those without an ICU stay), and from 61% to 91% (of those that included an ICU stay).

- for children aged 0 to 4 years, the average annual cost of bed days was approximately €10.4 million (range: €6 million to €17.5 million) for discharges that did not include an ICU stay, and €4.1 million (range: €2.6 million to €5.1 million) for discharges that included an ICU stay. This compares with a mean annual cost of €0.4 million (range: €0 to €1.3 million) in older adults for discharges that did not include an ICU stay.

- These data are likely an underestimate of the total burden of RSV, as not all RSV cases are laboratory confirmed and some discharges may not be coded. While there is an apparent trend of increasing incidence over time, this may reflect greater detection due to changes in testing practices for respiratory viruses and increased testing capacity since COVID-19 rather than a true increase in burden.

- As noted, palivizumab is currently offered to children identified to be at high risk of severe LRTD caused by RSV infection during their first and second RSV seasons. From 2019 and 2023, data from the Primary Care Reimbursement Scheme (PCRS) indicate that the number of children aged 0 to 4 years who have accessed palivizumab in primary care has ranged from 627 in 2021 to 768 in 2019.

- Uptake of existing immunisation programmes offered to infants (2018-2022), pregnant women and older adults was assessed to inform potential uptake of RSV immunisation strategies in these populations. There are comprehensive data to support uptake of the primary immunisation schedule (all vaccines) in infants (uptake range 87.2% to 90.0%) and for seasonal vaccines in older adults (seasonal influenza vaccination (2022-2023): 76.5%; COVID-19 vaccine: 99.4% -

primary course, 95.7% - first booster, 56.5% - 2023-2024 Autumn booster). However, there are very limited nationally collected data relating to uptake of vaccines routinely offered to pregnant women (seasonal influenza, COVID-19, pertussis) with data suggesting that uptake ranges from approximately 20% (COVID-19 vaccine) to a maximum of 62% (seasonal influenza vaccine).

    - Reported barriers to immunisation uptake in these populations include perceived low risk of illness, lack of knowledge or information, and concerns in relation to the effectiveness and safety of the vaccine.

- Data reported in this HTA relate to medically-attended cases that had laboratory testing to confirm RSV, with very limited data as to the burden of RSV among those who did not seek medical care. Moreover, there is currently a lack of data on the wider burden of RSV in Ireland and internationally. The limited international data available suggest that hospitalisation of a child negatively impacts parents' and or carers' health-related quality of life, job productivity and family health and functioning. In older adults, RSV has been reported to negatively impact the daily activities, productivity, social activities, relationships and employment of those infected.

- A costing analysis was conducted to estimate the potential costs and benefits associated with introducing an RSV immunisation programme in Ireland for the 2025-2026 RSV season, specifically considering strategies involving passive immunisation of children (through the use of either a directly acting monoclonal antibody, or through maternal vaccination) and the active immunisation of older adults.
- For children at increased risk of severe disease who are currently eligible for palivizumab, switching to nirsevimab was estimated to cost less than current care. Based on an ex-VAT unit cost of €301 for nirsevimab, the cost reductions for the 2025-2026 RSV season for these strategies were estimated at €0.85 million (-€1.24 million to -€0.52 million) for infants aged less than one year (n=240) and €2.07 million (-€2.94 million to -€1.35 million) if considering all eligible children aged less than two years (n=581).

- Of the three nirsevimab-based strategies directly targeting the general infant population, assuming an ex-VAT unit cost of €301 and an uptake rate of 88%, it was estimated that extending an RSV immunisation programme to include infants in the general population would cost for the 2025-2026 RSV season:

    - €9.3 million to procure and administer nirsevimab, with hospitalisation cost offsets of €6.8 million for the immunisation of infants born during the RSV season (n= 27,807; seasonal immunisation strategy)

  - €19.0 million to procure and administer nirsevimab, with hospitalisation cost offsets of €13.6 million for the immunisation of infants born during the RSV season and those entering their first RSV season (n= 55,678; seasonal and catch-up immunisation strategy)

  - €11.3 million to procure and administer nirsevimab with hospitalisation cost offsets of €8.1 million for the immunisation of infants aged less than four months between October and December (n=33,140; hybrid immunisation strategy).

- Offering a maternal immunisation strategy with RSVpreF to pregnant women who are expected to give birth during the RSV season (n=27,433) and assuming 62% uptake in this cohort and an ex-VAT unit cost of €165, it would cost €3.9 million to procure and administer RSVpreF for the 2025-2026 RSV season. These costs were estimated to be broadly comparable to the hospitalisation cost offsets for this strategy (incremental costs €0.01 million, 95% CI: -€2.24 million to €2.43 million).

- Four strategies considered seasonal vaccination of adults aged 65 years and older (n= 840,830 and assuming 76% uptake), or 75 years and older (n= 381,856 and assuming 87% uptake), with either RSVpreF or RSVPreF3. Assuming an ex-VAT unit cost of €165 for both vaccines, vaccination was estimated to cost for the 2025-2026 RSV season:

  - €146.0 million to procure and administer the vaccine for those aged 65 years and older, with hospitalisation cost offsets of €1.2 million for RSVpreF and €1.1 million for RSVPreF3.

  - €76.2 million to procure and administer the vaccine for those aged 75 years and older, with hospitalisation cost offsets of €1.0 million for RSVpreF and €0.9 million for RSVPreF3.

- In addition to the costs outlined above, there are implementation costs which would likely apply with the introduction of any new RSV programme for the general infant population or for older adults. These costs, including IT system updates, and information and training, would likely apply irrespective of the target populations considered and would not vary with immunisation uptake. The cost for the HSE's National Immunisation Office to implement a new programme is estimated at €2.3 million.

- The potential impact on health outcomes and healthcare utilisation of implementing an RSV immunisation programme is subject to considerable uncertainty. Key epidemiological parameters include immunisation coverage,

likelihood of hospitalisation and ICU admission, in addition to the clinical effectiveness of the available forms of RSV prophylaxis.

- The one-year total costs of these strategies are highly dependent on assuming a favourable product unit cost. Both the product unit costs and their relative costs should be a key consideration in any decision-making and in procurement negotiations with manufacturers.

- There would be substantial organisational challenges associated with extending RSV immunisation to the general infant and or older adult population. This includes potential existing staffing constraints and capacity issues in maternity hospitals and units if offering nirsevimab administration to newborns prior to discharge. In particular, there will be challenges in relation to the immunisation of older adults and those born outside the RSV season given the aim to maximise uptake within a short time frame (during the weeks immediately preceding the start of the anticipated RSV season). This considers the potential to offer immunisation to approximately:

    - 28,000 infants born outside of the RSV season in general practice or in maternity hospitals and units

    - 840,000 adults aged 65 years and older in primary care settings (general practice, community pharmacies and long-term care facilities).

- In the event of a decision to implement any of the immunisation strategies included in this assessment, consideration should be given to maximising uptake through public health information campaigns that raise awareness of RSV and immunisation options, empowering individuals and supporting informed decision-making.

- Options in terms of RSV immunoprophylaxis are changing rapidly considering that, to date, there is limited real-world evidence to support the effectiveness of the different strategies and that nirsevimab and the RSV vaccines are new active substances, and new biological medicines. Consideration should be given to data collection (for example, data relating to the immunisation status of RSV cases) to support ongoing monitoring and evaluation of the effectiveness of implemented strategies, to optimise outcomes and support efficient use of HSE resources.

- As requested by the Department of Health, this rapid HTA will be followed by a full HTA to inform a longer-term policy decision regarding RSV immunisation in Ireland.

Arising from the findings of this rapid HTA, HIQA's advice to the Minister for Health and the HSE is as follows:

- Respiratory syncytial virus (RSV) is a highly contagious seasonal virus. In healthy individuals, infection with RSV is usually self-limiting; however, complications can occur. Groups vulnerable to serious complications include infants, young children and older adults.
- RSV places a significant burden on secondary healthcare services, with the highest burden seen in infants aged less than one year. RSV poses a particular challenge for paediatric healthcare services as a high proportion of hospital discharges occur in quarter four each year. While testing capacity has increased, the identified data are likely an underestimate of the total burden, as not all RSV cases are laboratory confirmed and some discharges may not be coded.
- Given the recent authorisation of new technologies to reduce the burden associated with RSV (that is, the monoclonal antibody, nirsevimab, and the vaccines RSVpreF and RSVPreF3), international policies relating to immunisation against RSV in infants and adults are changing rapidly.
- International policy has been informed by RCT data and emerging observational data from countries that have implemented RSV immunisation for the 2023-2024 season, suggesting that these technologies are safe and effective.
- A costing analysis was undertaken for the 2025-2026 season for a range of potential immunisation strategies. These assumed an ex-VAT unit cost of €301 for nirsevimab and €165 for both RSVpreF and RSVPreF3 and considered potential cost offsets due to hospitalisations averted. Based on this, it was estimated that immunisation of:
    - children at increased risk of severe disease with nirsevimab instead of palivizumab would cost less than current care (€0.8 million less if considering eligible infants aged less than one year and €2.1 million less if considering all eligible children aged less than two years).
    - infants born during the RSV season with nirsevimab (assuming 88% uptake) would cost €9.3 million to procure and administer, with cost offsets of €6.8 million.
    - all infants (those born during the RSV season and those entering their first RSV season) with nirsevimab (assuming 88% uptake) would cost

€19.0 million to procure and administer, with cost offsets of €13.6 million.

  - infants aged less than four months between October and December with nirsevimab (assuming 88% uptake) would cost €11.3 million to procure and administer, with cost offsets of €8.1 million.
  - infants due to be born in the RSV season through maternal vaccination (assuming a maximum uptake of 62%) would cost €3.9 million to procure and administer, with cost offsets of €3.9 milllion.
  - all adults aged 65 years and older (assuming 76% uptake) would cost €146 million to procure and administer, with cost offsets of €1.2 million for RSVpreF and €1.1 million for RSVPreF3.
  - all adults 75 years and older (assuming 87% uptake) would cost €76.2 million to procure and administer, with cost offsets of €1.0 million for RSVpreF and €0.9 million for RSVPreF3.

- In addition to the costs of the various strategies as outlined, there are implementation costs which would likely apply with the introduction of any new RSV programme for the general infant population or for older adults. These programme costs, which would include IT system updates, information and training, would likely apply irrespective of the included target population(s) and or immunisation uptake. The cost for the National Immunisation Office to implement a new programme is estimated at €2.3 million.
- There is substantial uncertainty in relation to the potential costs associated with the RSV immunisation strategies included in this assessment. The one-year total costs of these strategies are highly dependent on assuming a favourable product unit cost. This should be a key consideration in any decision-making and in procurement negotiations with manufacturers.
- There would be substantial organisational challenges associated with extending RSV immunisation to the general infant and or older adult population, given the aim to maximise uptake within a short time frame (during the weeks immediately preceding the start of the anticipated RSV season). This considers the potential to offer immunisation to approximately:
  - 28,000 infants born outside of the RSV season in general practice or in maternity hospitals and units

- 840,000 adults aged 65 years and older in primary care settings (general practice, community pharmacies and long-term care facilities).

- In the event of a decision to implement any of the immunisation strategies included in this assessment, consideration should be given to:
  - maximising uptake through public health information campaigns that raise awareness of RSV and immunisation options, empowering individuals and supporting informed decision-making
  - data collection to support ongoing monitoring and evaluation of the effectiveness of the programme (for example, data relating to the immunisation status of RSV cases).

Executive Summary

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The aim of this rapid HTA was to provide advice to the Minister for Health and Health Service Executive (HSE), to inform an interim policy decision for one season (2025-2026 season) on the most appropriate RSV immunisation strategy for infants and or adults in Ireland. This advice was provided in the context of clinical recommendations from the National Immunisation Advisory Committee (NIAC) to the Department of Health. This rapid HTA considered the following domains:

- description of technology
- review of international practice
- epidemiology and burden of disease
- costing analysis.

Background

Respiratory syncytial virus (RSV) is a highly contagious ribonucleic acid (RNA) virus, which is transmitted through airborne respiratory droplets via coughing, sneezing or breathing. Primary infection with RSV can cause lower respiratory tract disease (LRTD) in infected individuals. In Ireland, RSV outbreaks typically occur in the winter months, with peaks observed in December and January, although RSV activity can peak earlier. Symptoms of RSV typically develop between four and seven days after infection, and can include respiratory symptoms (such as coughing, wheezing, sore throat, nasal drip and sneezing) and systemic symptoms (such as fever and reduced appetite). In healthy individuals, infection with RSV is usually self-limiting, and can be managed without medical attendance. However, RSV can cause more severe infections, such as pneumonia and bronchiolitis, which may lead to hospitalisation and could be fatal. RSV may also exacerbate chronic health conditions, in particular respiratory and circulatory conditions. Children at highest risk of serious LRTD include infants aged under six months, premature infants, children aged under two years with congenital heart or lung disease, children who are immunocompromised, and children with respiratory or neuromuscular disorders. Adults at highest risk of severe RSV include older adults (that is, those aged 65 years and older), particularly those with comorbidities (such as, chronic heart and lung disease), and those who are immunocompromised. Strategies for prevention of RSV in the general population typically focus on encouraging behaviours which may reduce virus transmission,

such as reducing social contacts when an individual is symptomatic, and encouraging good hand hygiene and respiratory hygiene practices.

Description of the technology

In Ireland, immunoprophylaxis against RSV is not currently offered to healthy infants and adults. Funding for palivizumab (Synagis®), a monoclonal antibody which offers passive immunisation against RSV, is provided by the Health Service Executive (HSE) for specified infant populations who are considered at high risk of serious complications of LRTD caused by RSV. Palivizumab is administered directly to the infant at monthly intervals during the RSV season (typically up to five doses). Two additional forms of passive immunisation for infants against RSV have been authorised in Europe. In October 2022, a long-acting monoclonal antibody, nirsevimab (Beyfortus®) was authorised which can be administered to the infant directly by intramuscular injection, with a single dose sufficient to infer protection against RSV for that season. In August 2023, a recombinant bivalent vaccine RSVpreF (Abrysvo®), or the "maternal vaccine", was authorised for use in pregnant women, which can provide infant protection through transplacental antibody transfer. Two vaccines have been authorised in Europe for the immunisation of adults aged 60 years and older, for prevention of LRTD caused by RSV: the recombinant bivalent vaccine RSVpreF (Abrysvo®), and the recombinant adjuvanted vaccine RSVPreF3 (Arexvy®). Nirsevimab, RSVpreF and RSVPreF3 are all subject to additional monitoring requirements by the European Medicines Agency, owing to the fact that they contain new active substances, and are new biological medicines.

Review of international practice

A review of international practice was undertaken to identify recommendations and policy with respect to the immunisation of infants and older adults against RSV in EU/EEA countries and the UK. A focus was placed on those countries where immunisation is currently offered, or planned to be offered, and whether or not it is publicly funded. It is important to note that nirsevmab and the RSV vaccines are not currently marketed in all the countries included in this review.

In Ireland, immunisation against RSV is recommended by NIAC for all infants in their first RSV season and for adults aged 65 years or older. Palivizumab is currently funded for infants at high risk of RSV-associated disease only, but nirsevimab is recommended to replace palivizumab for this cohort. A publicly-funded pilot (Pathfinder) that offers immunisation with nirsevimab is being implemented for all infants born during the 2024-2025 RSV season. For older adults, currently no RSV immunisation programme is in place, or planned, for the 2024-2025 RSV season.

Across the other 30 EU/EEA and UK countries, where information was identified regarding the passive immunisation of infants in the general population with nirsevimab and or the maternal vaccine, immunisation is consistently recommended by the relevant National Immunisation Technical Advisory Group (NITAG) or HTA body, but not necessarily funded by the relevant Ministry for Health or equivalent body. Five countries (Belgium, France, Germany, Spain and the UK) have publicly-funded immunisation programmes for the general infant population planned or in place for the 2024-2025 RSV season. All five countries will offer immunisation to all infants entering their first RSV season, irrespective of whether they were born during or outside of the RSV season. The programmes vary in terms of the method of immunisation, eligibility, the periods during which immunisation can be accessed, and priority groups for immunisation.

The UK will offer maternal vaccination (from 28 weeks gestation until delivery) on a year-round basis from 1 September 2024. In Spain and Germany, nirsevimab will be offered in the weeks prior to and during the RSV season (October to March). In Belgium and France, a choice of the maternal vaccine or nirsevimab will be offered. In cases where the pregnant woman receives the maternal vaccine less than two weeks before birth, the infant will also be eligible to receive nirsevimab. In Belgium, pregnant women (expected to deliver between September and March, inclusive) will be offered the maternal vaccine from 28 to 36 weeks gestation. Nirsevimab will be offered in the weeks prior to and during the RSV season (October to March). In France, the vaccine will be offered to women between 32 to 36 weeks gestation during the same window when nirsevimab is being offered (September to January, inclusive).

For the passive immunisation of infants at increased risk of LRTD associated with RSV, immunisation is widely recommended, but not necessarily funded. Until 2023, these recommendations were limited to palivizumab. Prior to the adoption of nirsevimab by five countries, the provision of palivizumab to those at increased risk of RSV-associated LRTD was funded (fully or partially) in 18 countries and also in Ireland. Of the five countries (Belgium, France, Germany, Spain and the UK) with publicly-funded RSV immunisation programmes planned or in place for the 2024-2025 RSV season, four (Belgium, France, Germany and Spain) preferentially recommend nirsevimab in place of palivizumab for infants and children at increased risk of RSV-associated LRTD. In the UK, these infants and children will be offered passive immunisation with palivizumab, regardless of whether the mother was vaccinated during pregnancy.

For the prevention of RSV-associated disease in older adults, two countries (the UK and Czech Republic) were identified to fully or partially fund RSV vaccines for older adults for the 2024-2025 season. In the UK, a publicy-funded vaccination

programme for all adults aged 75 to 79 years will be implemented from September 2024. In the Czech Republic, RSV vaccines are available (though not as part of an immunisation programme) on an individual basis for adults aged 60 years or older and are partially funded through insurance.

Of the five countries identified to have publicly-funded RSV immunisation programmes (for infants and or adults) planned or in place for the 2024-2025 RSV season, two (Belgium and Spain) have specified that their outlined approach to immunisation is for a single season with the intention to review their immunisation strategy for subsequent seasons. For the three other countries (France, Germany, and the UK), the outlined approach is not noted to be time limited, although all three highlight that the programmes may be updated in line with the latest evidence.

National recommendations in the countries examined were informed by the national and international epidemiology and burden of RSV, RCT data and emerging observational data from countries that have implemented RSV immunisation for the 2023-2024 season, suggesting that these technologies are safe and effective.

International practice with respect to immunisation of infants and older adults against RSV is a rapidly changing area. It is likely that there will be updates to national practices for the 2024-2025 RSV season and subsequent seasons, as further evidence becomes available.

Epidemiology and burden of disease

RSV incidence data were sourced from the Health Protection Surveillance Centre (HPSC) in Ireland for 2013 to 2023. Hospital utilisation data were sourced from the Hospital In-Patient Enquiry (HIPE) system for 2013 to 2022. For those aged 0 to 4 years, acute bronchiolitis data were also sourced from HIPE for the same period. Estimated averages exclude 2020 as these data are not considered representative due to the influence of the COVID-19 pandemic. Data typically were provided by calendar year rather than by RSV season.

The burden of RSV is substantially higher in infants aged less than one year compared with all other age bands examined as part of this assessment (those aged 1 to 4 and adults aged 65 years and older). Among those aged 0 to 4 years, infants aged less than one year accounted for, on average, 67% (range: 57% to 83%) of notified cases, 64% (range: 55% to 85%) of RSV-related ED attendances and 69% (range: 57% to 84%) of RSV-related hospital admissions. HPSC data relating to notified RSV hospital admissions for those aged 0 to 2 years were provided for the 2022-2023 season. Infants aged less than one year accounted for 69% (n=1,124) of notified hospital admissions, with 74% (n=834) of this burden in those aged less than six months (that is, 51% of all admissions in those aged 0 to 2 years occurred

in those aged less than six months). Among older adults, burden typically increased with age. Adults aged 80 years and older accounted for 46% (range: 35% to 48%) of notified cases, 43% (range: 40% to 46%) of RSV-related ED visits and 46% (range: 29% to 50%) of RSV-related hospital admissions.

HIPE data showed that, in those with a primary diagnosis of RSV, on average, each year there were 1,341 (range: 790 to 2,259) discharges that did not include an intensive care unit (ICU) stay (infants aged less than one year accounted for 84% of these discharges). The mean hospital length of stay (LOS) was four days and the mean total bed days associated with these discharges was 4,874 days (range: 3,118 to 7,377) per annum. Additionally, there were 121 (range: 62 to 201) discharges that included an ICU stay (infants aged less than one year accounted for 90% of these discharges). The mean hospital LOS was thirteen days and the mean total bed days associated with these discharges was 1,482 days (range: 926 to 1,956) per annum. Hospital discharges in quarter four accounted for the greatest proportion of annual discharges, ranging from 71% in 2018 to 91% in 2021 (of those without an ICU stay), and from 61% in 2018 to 91% in 2021 (of those that included an ICU stay). The average cost of bed days was approximately €10.4 million per annum (range: €6 million to €17.5 million) for discharges that did not include an ICU stay, and €4.1 million (range: €2.6 million to €5.1 million) for discharges that included an ICU stay.

HIPE data indicate that in adults aged 65 years and older, the number of discharges was relatively low. From 2013 to 2022, there were a total of 225 discharges and 2,154 bed days (of which 134 and 1,302 were recorded in 2022, respectively). Discharges that included an ICU stay were uncommon, with fewer than five discharges a year recorded in those aged 65 years and older in all but one of the years over this time period. The mean annual cost associated with hospital discharges that did not include an ICU stay was €0.4 million, although these data are highly skewed (range: €0 to €1.3 million).

Annual RSV-related mortality rates have been consistently low. In those with a primary diagnosis of RSV, rates ranged from 0.0 to 0.9 per 100,000 in those aged 0 to 4 years. In those aged 65 years and older, the majority of annual mortality data were suppressed due to small count numbers (1 to 5), with no deaths reported in 2013. The highest rate was reported in 2022 (2.4 per 100,000; n=19).

These data are likely an underestimate of the total burden of RSV, as not all RSV cases are laboratory confirmed and some discharges may not be coded. While there is an apparent trend of increasing incidence over time, this may reflect greater detection rather than a true increase in burden. Moreover, there is currently a lack of data on the wider burden of RSV in Ireland and internationally. The limited

international data available report that hospitalisation of a child negatively impacts parents' and or carers' health-related quality of life, job productivity and family health and functioning. In older adults, RSV has been reported to negatively impact the daily activities, productivity, social activities, relationships and employment of those infected.

Costing analysis

A costing analysis was conducted to estimate the potential costs and benefits associated with introducing an RSV immunisation programme in Ireland, specifically considering strategies involving passive immunisation of children (through the use of either a directly acting monoclonal antibody, or through maternal vaccination), and the active immunisation of older adults. Assuming that nirsevimab has the same efficacy as palivizumab, offering immunisation with nirsevimab to children at increased risk of severe disease associated with RSV, who are currently eligible for immunisation with palivizumab, would cost less than current care. Based on a cost per unit of €301.12 for nirsevimab, the cost reductions for these strategies for infants aged less than one year were estimated at €0.85 million (-€1.24 million to -€0.52 million) and €2.07 million (-€2.94 million to -€1.35 million) in children aged less than two years.

Of the three immunisation strategies directly targeting the general infant population using nirsevimab, assuming an ex-VAT cost of €301.12 per unit and an uptake rate of 88%, it was estimated that extending an RSV immunisation programme to include infants in the general population would cost for the 2025-2026 RSV season:

- €9.3 million to procure and administer nirsevimab, with cost offsets of €6.78 million for the immunisation of infants born during the RSV season (seasonal immunisation strategy)
- €19.0 million to procure and administer nirsevimab, with cost offsets of €13.55 million for the immunisation of infants born during the RSV season and those entering their first RSV season (seasonal and catch-up immunisation strategy)
- €11.3 million to procure and administer nirsevimab with cost offsets of €8.08 million for the immunisation of infants aged less than four months between October and December (hybrid immunisation strategy).

Offering a maternal immunisation strategy with RSVpreF to pregnant women who are expected to give birth during the RSV season (assuming 62% uptake in this cohort, and an ex-VAT cost of €165.00 per unit RSVpreF) would cost €3.9 million to procure and administer for the 2025-2026 RSV season. These costs were estimated

to be broadly comparable to the hospitalisation cost offsets for this strategy (incremental costs €0.01 million, 95% CI: -€2.24 million to €2.43 million).

While costing a range of combination strategies was considered beyond the scope of this analysis, a scenario analysis was conducted to estimate potential upper and lower bounds of expenditure associated with offering a combination strategy to those infants born during the RSV season, considering both maternal immunisation with RSVpreF at varying vaccine uptake rates (30% and 60%), and offering nirsevimab to the remaining eligible infant cohort. If a combination strategy was offered, and assuming 30% maternal immunisation uptake, the total cost of achieving 88% immunisation coverage in infants born during the RSV season was estimated to be between €6.23 million (if nirsevimab was procured at a unit cost of €209), and €9.9 million (if nirsevimab was procured at a unit cost of €393.24). If a combination strategy was offered, and assuming 60% maternal immunisation uptake, the total cost of achieving 88% immunisation coverage in infants born during the RSV season was estimated to be between €5.88 million (if nirsevimab was procured at a unit cost of €209), and €7.65 million (if nirsevimab was procured at a unit cost of €393.24).

Four strategies considered seasonal immunisation of adults aged 65 years and older (assuming 76% uptake), or 75 years and older (assuming 87% uptake), with either RSVpreF or RSVPreF3. Assuming an ex-VAT cost of €165.00 per unit for both vaccines, vaccination was estimated to cost for the 2025-2026 RSV season:

- €146.0 million to procure and administer the vaccine for those aged 65 years and older, with hospitalisation cost offsets of €1.2 million for RSVpreF and €1.1 million for RSVPreF3.
- €76.2 million to procure and administer the vaccine for those aged 75 years and older, with hospitalisation cost offsets of €1.0 million for RSVpreF and €0.9 million for RSVPreF3.

In addition to the costs of the various strategies as outlined, there are implementation costs which would likely apply with the introduction of any new RSV programme for the general infant population or for older adults. These costs, which would include IT system updates, information and training, would likely apply irrespective of the target population(s) considered and would not vary with immunisation uptake. The cost for the HSE's National Immunisation Office to implement a new programme is estimated at €2.3 million.

The potential impact on health outcomes and healthcare utilisation of implementing an RSV immunisation programme is subject to considerable uncertainty. Key epidemiological parameters include immunisation coverage, likelihood of

hospitalisation and ICU admission, in addition to the clinical effectiveness of the available forms of RSV prophylaxis. Key costs include the estimated costs of the technologies considered and the associated administration fees and labour costs. The one-year total costs of these strategies is highly dependent on assuming a favourable product unit cost. Both the product unit costs and their relative costs should be a key consideration in any decision-making and in procurement negotiations with manufacturers. These cost estimates are subject to substantial uncertainty and further real-world evidence may help to reduce this uncertainty.

Conclusions

The burden of RSV in infants and older adults is substantial, with the largest healthcare utilisation burden observed for infants aged less than one year. However, there is considerable uncertainty in relation to the potential impact of implementing an immunisation programme against RSV; this uncertainty relates primarily to the potential acquisition price and fees associated with the different forms of immunisation.

Plain language summary

Respiratory syncytial virus (RSV) is a virus that infects the lungs and upper airways. This virus spreads every winter, with the RSV season in Ireland typically running from October to March. In healthy people, infection with RSV can be managed without needing to see a doctor. However, RSV can cause more severe infections in some people, which may lead to them being hospitalised. People at increased risk of severe disease include infants aged under one year, premature babies and children aged under two years with certain medical conditions. Adults aged 65 years and older are also at increased risk of severe disease.

Curently in Ireland, a small number of children who are at high risk of severe disease are offered a drug called palivizumab (Synagis®) to protect them from RSV. Since 2022, a new drug called nirsevimab (Beyfortus®) and two new RSV vaccines have been approved. These can be used to protect infants in the general population and older adults from RSV, not just children who are at high risk. Palivizumab and nirsevimab are not vaccines. They are laboratory-made antibodies which stimulate the immune system, so to provide protection against RSV. While palivizumab has to to be administered monthly during the RSV season, nirsevimab is long-acting, meaning only one dose is needed to protect infants for the RSV season. One of the vaccines can be given to pregnant women — antibodies from the mother transfer to the baby to provide protection from RSV up to six months of age.

In Ireland, nirsevimab (Beyfortus®) will be offered to infants born between September 2024 and February 2025 in a temporary, publicly-funded pilot programme. The Department of Health asked the Health Information and Quality Authority (HIQA) to look at the impact of immunising all infants and older adults with these new drugs to help to inform a decision for the 2025-2026 season. This assessment looked at the benefits and costs to the Health Service Executive (HSE) for differing approaches to immunisation. A larger assessment will be conducted after this assessment is completed, to provide advice for a longer-term policy decision about RSV — this will include the emerging international evidence and evidence from the pilot programme.

We looked to see what other European countries recommend regarding the protection of infants and older adults against RSV. Five of the 31 countries included in this assessment have publicly funded at least one of these new drugs or vaccines to protect infants and or older adults against RSV disease during the 2024-2025 RSV season. Several countries are currently undertaking their own assessment to determine whether they will be funded or not. These national and international recommendations were informed by results from large randomised controlled trials

and real-world evidence from international programmes for the 2023 to 2024 RSV season. This evidence suggests that nirsevimab and the new RSV vaccines are safe and effective in reducing the burden from RSV.

The number of people diagnosed with RSV and the number who require hospitalisation varies from year to year. In 2022, almost 4,000 children in Ireland aged 0 to 4 years tested positive for RSV. Of these, almost 2,500 were admitted to hospital. The majority of these admissions, and almost all ICU admissions, were in children aged less than one year. Most of these hospital admissions happen over a short time period (between October and December). This makes it very challenging for the hospitals and can disrupt routine care (for example, planned surgeries) for other children. In 2022, there were just over 1,500 adults in Ireland aged 65 years and older who tested positive for RSV. Of these, almost 150 were admitted to hospital.

We looked at the cost of immunising different groups of infants and older adults for the 2025-2026 RSV season. For the small number of children at high risk of RSV, we found that it would cost less to switch from palivizumab to the nirsevimab. It would also be more convenient for these families as only one injection would be needed. We found that the cost of immunising infants would range from €3.9 million to €19 million depending on the approach taken. It is expected that these costs would be partially offset by the fact that fewer infants would require hospital care. We found that the cost of vaccinating older adults would be much higher due to the large number of people involved. Offering the vaccine to everyone aged 65 years and older was estimated to cost €146 million, while it would cost €76.2 million if only offered to those aged 75 years and older. As the number of older people who are hospitalised due to RSV is relatively small, the potential cost savings to the HSE from reducing hospital admissions is also small (between €0.9 million and €1.2 million). It is important to note that to calculate these estimates, we have had to assume prices for these drugs, based on known Irish and international prices. If the price of any of these drugs is in fact higher than we have estimated, the costs of immunisation will also be higher. Aside from the cost of providing immunisation to these infant and older adult groups, there would also be additional costs associated with organising any RSV immunisation programme, which we estimated could cost approximately €2.3 million.

In summary, one new drug and two new vaccines have recently been licensed for use in infants and older adults, which may protect them from RSV. However, while the evidence to date indicate that they are safe and effective, the real-world evidence is limited as these are new products. There is still a lot of uncertainty about the potential costs of these new products and the potential to reduce the burden on the healthcare service.

If the Government decides to fund RSV immunisation and roll out programmes for infants or older adults, there are important things to consider about who might administer these products and where this might happen. For example, if a decision is taken to immunise all infants in their first RSV season, options could include that the roll out is supported by GPs or by special hospital clinics. The timing of administration is also very important. In order to get the best outcomes, some of the products must be given in the weeks before the RSV season begins. Organising the administration of these products to a large number of infants and older adults in this short time frame may be very difficult.

List of abbreviations used in this report

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices (US)
ADA	anti-drug antibodies
ALRI	acute lower respiratory tract infection
ARI	acute respiratory infection
BCG	Bacillus Calmette-Guérin vaccine
BPD	bronchopulmonary dysplasia
CAD	Canadian dollar
CDC	Centers for Disease Control and Prevention (US)
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIDR	Computerised Infectious Disease Reporting system
CLD	chronic lung disease
COVID-19	coronavirus disease 2019
CPGs	Clinical Practice Guidelines
CSMI	Higher Council for Infectious Diseases (Luxembourg)
CSO	Central Statistics Office
DNA	deoxyribonucleic acid
DPS	Drug Payment Scheme
EAG	expert advisory group
ECDC	European Centre for Disease Prevention and Control
ECFNI	European Foundation for the Care of Newborn Infants

ED	emergency department
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERVISS	European Respiratory Virus Surveillance Summary
EU	European Union
FDA	Food and Drug Administration (USA)
G-BA	Federal Joint Committee (Germany)
GBD	Global Burden of Disease
GMS card	General Medical Services card
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS	Haute Autorité de Santé (France)
HIPE	Hospital In-Patient Enquiry system
HIQA	Health Information and Quality Authority
HIV	human immunodeficiency virus
HPO	Healthcare Pricing Office
HPSC	Health Protection Surveillance Centre
HR-QoL	health-related quality of life
HS-CHD	hemodynamically significant congenital heart disease
HSE	Health Service Executive
HTA	health technology assessment
ICGP	Irish College of General Practitioners
ICU	intensive care unit
IHI	individual health identifier

ILI	influenza-like illness
INSPIRE	Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure
IQR	interquartile range
IV fluids	intravenous fluids
JCVI	Joint Committee on Vaccination and Immunisation
KCE	Knowledge Exchange and Care Centre (Belgium)
LHO	Local Health Offices
LOS	length of stay
LRTI / LRTD	lower respiratory tract infection / lower respiratory tract disease
LTCF	long-term care facilities
mABs	monoclonal antibodies
MAE	medically-attended adverse event
MATISSE	Maternal Immunisation Study for Safety and Efficacy
NCCS	HSE National Cold Chain Service
NCIRD	National Center for Immunization and Respiratory Diseases (US)
NHCP	National Healthy Childhood Programme
NHS	National Health Service
NIAC	National Immunisation Advisory Committee
NIO	National Immunisation Office
NITAG	National Immunisation Technical Advisory Group
NNBSP	National Newborn Bloodspot Screening Programme
NPRS	National Perinatal Reporting System
NVRL	National Virus Reference Laboratory

OR	odds ratio
OWSA	one-way sensitivity analysis
PCCU	paediatric critical care unit
PCRS	Primary Care Reimbursement Service
PI	prediction interval
PICo	population, area of interest and context
PICU	paediatric intensive care unit
PHN	public health nurse
PPSN	personal public service number
PRAC	Pharmacovigilance Risk Assessment Committee
PROMISE	Preparing for RSV Immunisation and Surveillance in Europe
QALY	quality-adjusted life year
QIV	quadrivalent influenza vaccine
RCT	randomised controlled trial
RESCEU	REspiratory Syncytial virus Consortium in Europe
RESMA	responding to an emergency situation and management of anaphylaxis
RIVM	National Institute for Public Health and the Environment (The Netherlands)
RNA	ribonucleic acid
RR	relative risk / risk ratio
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcriptase-polymerase chain reaction
R_0	basic reproductive number

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCID	severe combined immunodeficiency
SHC	Superior Health Council (Belgium)
SIIV	seasonal inactivated influenza vaccine
SmPC	Summary of Product Characteristics
STIKO	the Standing Committee on Vaccination (Germany)
Tdap	tetanus, diphtheria and acellular pertussis vaccine
TESSy	European Surveillance System
THL	Institute of Health and Welfare (Finland)
UK	United Kingdom
UKHSA	UK Health Security Agency
US	United States
VAERS	Vaccine Adverse Reporting System
VAT	Value-added tax
VSD	Vaccine Safety Datalink
wGA	weeks gestational age
WHO	World Health Organization
WHO/Europe	World Health Organization Regional Office for Europe

1 Introduction

1.1 Background to the request

Respiratory syncytial virus (RSV) is a common pathogen and major contributor to acute lower respiratory tract infections (ALRIs) in children and older adults. RSV is a single-stranded RNA virus belonging to the *Orthopneumovirus* genus of the family *Pneumoviridae*.[1] RSV has one serotype with two antigenic subgroups, A and B. The antigenic subgroups are defined by their reactivity to monoclonal antibodies (mAbs).[2] Both subtypes may co-circulate during a season, with alternating predominance of RSV A and RSV B depending on the season.[3] In a 2022 systematic review of the global distribution of RSV A and B infections, RSV A has been identified as the predominant strain in most years, but regional and seasonal differences are common.[4]

RSV epidemics occur during the winter months in temperate regions.[2] RSV infection is common in children and most have been infected with RSV by the time they are two years old. Reinfection throughout a person's lifetime is common, but disease severity tends to be reduced with repeated exposure.[5] Most infections in children are mild and lead to 'flu-like' symptoms often accompanied by otitis media. However, in some children, infection may result in bronchiolitis, pneumonia and croup.[5] Infants aged six months and younger are at higher risk of hospitalisation and serious outcomes.[2] Furthermore, RSV infection has been implicated in asthma pathogenesis.[2] In older children and adults, symptoms are generally either absent or confined to the upper respiratory tract.[5] Older adults, those who are immunocompromised and those with chronic cardiopulmonary disease are also at increased risk of severe disease, with RSV infection contributing to significant morbidity and mortality in this population.[5]

In most healthy individuals, RSV is self-limiting and the mainstay of treatment is supportive — for example, antipyretics, adequate fluid intake and rest. The emphasis remains on prevention of RSV infection as the main therapeutic approach to managing this disease.[6] Non-pharmaceutical measures to prevent RSV infection include frequent handwashing, respiratory hygiene and cleaning contaminated surfaces such as door handles. In the hospital setting, RSV transmission can be prevented by managing patients with RSV on the same ward, use of barrier precautions (for example, gowns and gloves) and restricting visiting.

Regarding pharmaceutical interventions to prevent RSV infection, these can be classified as: a) passive immunisation with monoclonal antibodies (mAB) or maternal vaccination during pregnancy; and b) active immunisation with vaccines designed for older adults.[6] In Europe, as of 1 June 2024, there are three forms of passive

immunisation approved to reduce the risk of RSV disease in infants. Firstly, palivizumab (Synagis®),[7] authorised by the European Medicines Agency (EMA) in August 1999; secondly, nirsevimab (Beyfortus®),[8] authorised by the EMA in October 2022; and thirdly, RSVpreF (Abrysvo®),[9] authorised by the EMA in August 2023. The latter, RSVpreF (Abrysvo®),[9] is also approved for active immunisation of adults aged 60 years and older. Additionally, RSVPreF3 (Arexvy®),[10] authorised by the EMA in June 2023, is another vaccine approved for the prevention of RSV-related lower respiratory tract disease in adults aged 60 years and older.

Given the recent authorisation of nirsevimab, RSVpreF and RSVPreF3, many countries are considering changes to their policies relating to immunisation against RSV in infants and adults. In October 2023, the National Immunisation Advisory Committee (NIAC) issued recommendations to the Department of Health in Ireland regarding immunisation against RSV.[11] NIAC recommends the passive immunisation of all infants against RSV during their first RSV season. They also recommend that once available, nirsevimab should replace palivizumab for those high-risk infants and children who are currently eligible to receive palivizumab.[11] Regarding adults, NIAC recommends active immunisation of all adults aged 65 years and older with either RSVPreF3 or RSVpreF. Additionally, NIAC has suggested that an analysis of the cost effectiveness of different programmatic considerations be undertaken to determine the most appropriate use of immunisation against RSV in Ireland.

The Department of Health requested that HIQA complete a rapid health technology assessment (HTA) of alternative infant and adult immunisation strategies against RSV in Ireland to inform an interim policy decision on the most appropriate RSV immunisation strategy for infants and or adults for one season (that is, the 2025-2026 season). Due to the short timeline within which the information needs to be provided, the rapid HTA was limited to a restricted number of domains. Following completion of the rapid HTA, a full HTA including a systematic review of the clinical effectiveness and safety of RSV immunisation and de novo economic modelling of alternative immunisation strategies will be undertaken to inform a potential longer term change to the immunisation programme. On 18 June 2024, the Minister for Health announced the RSV Immunisation Pathfinder Programme which is being piloted for the 2024-2025 season.[12] Through this programme, parents of babies (limited to those born from September 2024 to February 2025) will be encouraged to have their babies immunised with nirsevimab before leaving the maternity unit.

1.2 Terms of reference

The HTA was submitted as advice to the Minister for Health and Health Service Executive (HSE) to inform an interim policy decision for one season (2025-2026 season) on the most appropriate RSV immunisation strategy for infants and or adults

in Ireland. This advice was provided in the context of the clinical recommendations provided by NIAC to the Department of Health. In consultation with the Department of Health, HIQA's Evaluation Team developed a set of objectives with consideration to the evidence needs of the decision-maker.

The terms of reference for the rapid HTA, agreed with the Department of Health, were to:

- Describe the forms of RSV immunisation authorised for use.
- Summarise current RSV immunisation recommendations and immunisation programmes in EU/EEA countries and the UK and the evidence underpinning these recommendations and or programmes.
- Describe the epidemiology and burden of disease associated with RSV in children aged less than four years and in adults aged 65 years and older in Ireland.
- Describe the uptake of immunisation against RSV in EU/EEA countries and the UK.
- Describe the uptake of other seasonal vaccines (influenza and COVID-19) in Ireland. Specific subgroups of interest are:
    - pregnant women (to also include uptake of antenatal pertussis, that is, whooping cough vaccine)
    - adults aged 65 years and older.
- Provide an indication of the likely additional costs associated with different immunisation strategies against RSV in Ireland.
- Based on the evidence in this assessment, provide advice to the Minister for Health and the HSE to inform an interim policy decision for one season (2025-2026 season) on the most appropriate RSV immunisation strategy for infants and or adults in Ireland.

1.3 Overall approach

Following an initial scoping of the available evidence, the terms of reference of this assessment were agreed between HIQA and the Department of Health. HIQA appointed an evaluation team comprising staff from the HTA Directorate to carry out the assessment.

HIQA convened an expert advisory group (EAG) comprising representation from relevant stakeholders, including patient representation, decision-makers, clinical experts, public health experts and methodological expertise. The role of the EAG was to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the EAG is available in the EAG membership section of this report.

The terms of reference for the EAG were to:

- Contribute to the provision of high quality and considered advice by HIQA to the Minister for Health and the HSE
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to HIQA regarding the scope of the analysis.
- Support the Evaluation Team led by HIQA during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process upon the conclusion of the assessment.

The terms of reference of the HTA were reviewed by the EAG at their meeting. The draft protocol and draft chapters on the description of the technology, review of international practice, epidemiology and burden of disease, and costing analysis were circulated to the EAG and discussed at that meeting. Following the incorporation of feedback, a revised draft of the completed report was circulated for review by the EAG and amended, as appropriate. Following its approval by HIQA's Executive Management Team, the completed assessment was submitted to the Minister for Health and the HSE as advice and published on the HIQA website.

2 Description of technology

Key Points

- Respiratory syncytial virus (RSV) is a highly contagious ribonucleic acid (RNA) virus, which is transmitted through airborne respiratory droplets via coughing, sneezing or breathing. Primary infection with RSV can cause lower respiratory tract disease (LRTD) in infected individuals. RSV has been a notifiable disease in Ireland since 2012.
- In Ireland, RSV outbreaks typically occur in the winter months, with the highest number of infections usually reported in December and January, although RSV activity can peak earlier.
- In healthy individuals, infection with RSV is usually self-limiting, and can be managed without medical attendance. However, RSV can cause more severe infections, such as pneumonia and bronchiolitis, which can lead to hospitalisation and which can be fatal. RSV may also exacerbate chronic health conditions, in particular respiratory and circulatory conditions.
- Children at highest risk of serious LRTD caused by RSV include infants aged under six months, premature infants, children aged under two years with congenital heart or lung disease, children who are immunocompromised, and children with respiratory or neuromuscular disorders.
- Adults at highest risk of severe RSV include older adults (that is, those aged 65 years and older), particularly those with comorbidities (such as chronic heart and lung disease), and those who are immunocompromised.
- Strategies for prevention of RSV in the general population typically focus on encouraging behaviours which may reduce virus transmission, such as reducing social contacts when an individual is symptomatic, and encouraging good hand hygiene and respiratory hygiene practices.
- In Ireland, immunoprophylaxis against RSV is not currently offered to healthy infants and adults. Funding for palivizumab (Synagis®), a monoclonal antibody which offers passive immunisation against RSV, is provided by the Health Service Executive (HSE) for specified infant populations who are considered at high risk of serious complications of lower respiratory tract disease caused by RSV. Palivizumab is administered directly to the infant at monthly intervals during the RSV season (typically up to five doses).
- Two additional forms of passive immunisation for infants against RSV have been authorised in Europe.

- In October 2022, a long-acting monoclonal antibody, nirsevimab (Beyfortus®) was authorised which can be administered to the infant directly by intramuscular injection, with a single dose sufficient to infer protection against RSV for that season.
- In August 2023, a recombinant bivalent vaccine RSVpreF (Abrysvo®) was authorised for use in pregnant women, to provide passive immunisation of infants from birth to six months of age through transplacental antibody transfer.

- Two vaccines have been authorised in Europe for the immunisation of adults aged 60 years and older, for prevention of LRTD caused by RSV: the recombinant bivalent vaccine RSVpreF (Abrysvo®), and the recombinant adjuvanted vaccine RSVPreF3 (Arexvy®).
- Nirsevimab, RSVpreF and RSVPreF3 are all subject to additional monitoring requirements by the European Medicines Agency, owing to the fact that they contain new active substances, and are new biological medicines.

2.1 Introduction

The purpose of this chapter is to describe forms of immunisation authorised for use in Ireland to protect infants and older adults against respiratory syncytial virus (RSV). This chapter provides background on RSV's potential as a pathogen, and the resulting disease and related complications which may occur as a consequence of infection. These will be explored in greater detail in Chapter 4. This chapter also provides an overview of the current treatment and prevention of RSV in Ireland, and a description of national recommendations for immunisation of infants and older adults against RSV. Details of international recommendations and implemented RSV immunisation programmes for infants and older adults are outlined in greater detail in Chapter 3.

2.2 Pathogen

RSV is a negative-sense, single-stranded ribonucleic acid (RNA) virus that belongs to the genus Orthopneumovirus within the family Pneumoviridae.[13] RSV has a non-segmented genome, meaning that reassortment of genome segments cannot occur. As such, RSV cannot not undergo antigenic shifts which could cause pandemics, as is the case for the influenza virus.[14]

Two major antigenic subtypes of RSV exist in humans, RSV-A and RSV-B, though the clinical significance of these subtypes is unclear.[15] RSV-A is generally more prevalent than RSV-B, and of the two subtypes, RSV-A is associated with a higher

viral load.[13] These antigenic subtypes are determined by variation in the structure of the viral membrane proteins. RSV uses two of these membrane proteins, which are present on its surface, to attach or fuse to host cells and initiate infection. Glycosolated attachment protein (G) enables the virus to attach to the respiratory epithelial cells of the host, while fusion protein (F) fuses the viral and host cell membranes, allowing viral RNA to enter the targeted cell where replication subsequently occurs.[16] The 'G protein' shows substantial antigenic and genomic variability between RSV-A and RSV-B strains, and it is this variability which enables the virus to evade the host's immune response.[17] It is responsible for both the initial pathogenicity of the virus and for increasing its potential for reinfection. In contrast, given its pivotal role in viral transmission and infection, and the fact that it is highly conserved between RSV-A and RSV-B strains, the prefusion conformation of the 'F protein' has been an obvious target in the development of forms of immunisation against RSV.

RSV is highly contagious with an estimated basic reproductive number (R_0) of 3.0.[18] The R_0 of an infectious disease refers to the expected number of infections generated by one case in a completely susceptible population. As such, in a completely susceptible population, it is expected that one case of RSV could infect three other individuals.[19] RSV is spread by large droplets and secretions from contact with an infected person. RSV can also survive on hard surfaces such as worktops and doorknobs for up to six hours. The incubation period (that is, the time between exposure and when symptoms are first apparent) for RSV ranges from four to seven days. Infected individuals remain contagious as long as the virus is being shed (that is, the release of virus progeny following successful reproduction during a host cell infection), with differences in the duration of the infectious period depending on age, severity of infection and health status. Shedding can start one or two days before the onset of symptoms.[14] In general, infants shed the virus for up to 14 days in mild infections; however, in those with severe infection or in those aged less than six months, the virus may shed for up to three weeks. Additionally, immunocompromised individuals may shed the virus for several months following infection. Infants typically experience mild to moderate nasal congestion and low-grade fever within a few days of exposure, followed by a productive cough. Viral bronchiolitis is one of the most common viral illnesses that occurs in infants as a result of RSV infection. In older people, the symptomatic profile is similar to that seen in infants, although there is increased likelihood of lower respiratory tract involvement. Clinical presentation observed in older people can vary from cold-like symptoms to acute respiratory distress.[14]

In Ireland, RSV outbreaks typically occur between October and March. The highest number of infections are typically reported in December and January, although RSV activity can peak earlier. For example, during the 2021-2022 season, cases peaked

in mid-November 2021. Internationally, seasonality may vary from year to year, such as that seen during the COVID-19 pandemic.[20, 21] The shifts in seasonality for more recent RSV seasons cannot be definitively explained.[22] It is unclear whether the seasonal variation observed over recent seasons are unique events, or if they indicate future changes or unpredictability in RSV seasonal patterns. Furthermore, internationally, methods and assessment characteristics used to define RSV seasonality have been found to differ, leading to challenges interpreting study results.[23] The incidence and seasonality of RSV in Ireland are described in Chapter 4.

RSV has been listed as a notifiable disease in Ireland since 2012, with RSV activity monitored by the Health Protection Surveillance Centre (HPSC). It can be detected through laboratory testing, with reverse transcriptase-polymerase chain reaction (RT-PCR) assays considered the most reliable form of testing at present. Other methods of detection include antigen testing and viral isolation.[22] However, true incidence is likely under-estimated as those infected commonly experience mild symptoms which are easily managed without medical attendance. Additionally, levels of RSV infection in older adults may be under-reported, as they tend to have lower viral loads present in their respiratory specimens and as such, the laboratory tests are not always sensitive enough to detect infection in this population.[15] Most people will only find out they have RSV if they are receiving treatment in hospital.[22]

While it is estimated that 95% of children will have become infected with RSV at least once before they reach two years of age,[13] immunity to RSV is short-lived. Repeated infections may occur throughout the life course, though with increasing age, both the likelihood of reinfection and severity of infection is reduced. However, certain groups (for example, older adults) remain at greater risk of severe RSV if infected.[5]

2.3 Disease

Symptoms of RSV typically develop between four and seven days after infection. RSV may present through both respiratory symptoms (such as coughing, wheezing, sore throat, nasal drip and sneezing) and systemic symptoms (such as fever and reduced appetite).[22, 24] Symptoms such as otitis media and croup may also be experienced by infants and young children.[22] Symptoms may not develop concurrently, and may appear in stages.[25] In some instances, breathing difficulties and fatigue or irritability may be the only symptoms of infection.[22, 25]

In healthy adults and older children, RSV is typically limited to mild respiratory symptoms, which will not require medical attention. In some cases, RSV can cause more severe disease, such as pneumonia and bronchiolitis (where the small airways of the lungs become inflamed),[25] which may lead to hospitalisation and could be

fatal. RSV is the most common cause of pneumonia and bronchiolitis in infants aged under one year, and the most common cause of hospital admissions due to acute respiratory illness in children aged under five years.[22] The burden of hospitalisations associated with RSV in Ireland is described in detail in Chapter 4.

Infection with RSV can exacerbate chronic health conditions, and may also lead to other long-term sequelae as a consequence of the resulting lower respiratory tract disease. For example, those with asthma may experience asthma attacks as a consequence of RSV infection,[26] and there is a well-documented association between severe RSV infection in early life and the development of recurrent wheeze of early childhood or asthma later in life, though causality has not yet been established.[13, 27] At present, it is unclear whether early-life infection with RSV increases the risk of asthma developing in the affected infant, or whether severe early-life infection with RSV is a marker for those with an underlying genetic predisposition for developing asthma.[28] A prospective, US population-based study (published in 2023) sought to control for this genetic variability by determining the RSV infection status in a cohort of healthy infants within their first year of life. The study found an age-dependent association between RSV infection in the first year of life, and childhood asthma. Additionally, children not infected with RSV in infancy had a 26% lower risk of five-year current asthma than those infected with RSV in infancy; adjusted relative risk (RR) 0.74, 95% confidence interval (CI) 0.58 to 0.94.[29]

Children at highest risk of severe RSV include:

- infants aged under six months
- premature infants (that is, infants born before 37 completed weeks of gestation)
- children aged under two years with congenital heart or chronic lung disease
- children who are immunocompromised
- children with respiratory or neuromuscular disorders.[22]

Adults at highest risk of severe RSV include those:

- aged 65 years and older
- with comorbidities, including those with chronic heart and lung disease
- who are immunocompromised.[22]

Co-infection with other respiratory viruses (such as SARS-CoV-2 and influenza) is possible, as infection with one virus may lower the immunity of an infected individual, rendering them more susceptible to infection with another pathogen. In addition, while both influenza and RSV circulate year-round, they are classified as 'winter' viruses, due to the seasonal nature of their circulatory patterns and

outbreaks.[30] Given the increase in cases observed for both viruses over the winter period, it would be expected that the likelihood of co-infection would be increased. Furthermore, post-pandemic COVID-19 transmission has been found to follow a similar seasonal pattern to these winter respiratory viruses in both Europe and the US,[31] which could also increase the likelihood of co-infection. However, there is limited evidence to inform the extent to which co-infection with another respiratory virus impacts patient morbidity.[11] One systematic review and meta-analysis which considered the severity of respiratory illness in children infected with RSV alone compared with those co-infected with RSV and any other virus, found an association between co-infection with RSV and RSV-human metapneumovirus only, where co-infection was linked with a significantly higher risk of ICU admission (odds ratio (OR) 7.2, 95% CI: 2.1 to 25.1).[32]

Respiratory viruses, including RSV, can also predispose an infected individual to bacterial co-infection or secondary bacterial infection. There are a number of mechanisms which enable this, including altered immune response, physical damage to airway epithelial cells, and disrupted mucociliary clearance,[33] all of which ultimately reduce respiratory function and promote colonisation of bacteria. Viral infection of the lower respiratory tract is also a risk factor for bacterial superinfection, with increasing incidence of bacterial superinfection observed with increasing severity of respiratory illness.[34]

2.4 Treatment of RSV and RSV-associated lower respiratory tract disease

In healthy individuals, RSV typically presents as a self-limiting disease. As such, supportive care, such as symptomatic treatment with antipyretics (such as paracetamol and ibuprofen) and over-the-counter cough and cold preparations (where age appropriate), is often the most appropriate way to manage the disease, in addition to maintaining adequate fluid intake.[6] In cases where symptoms are more severe, or where dehydration or serious secondary infection is suspected, hospitalisation may be necessary. In such instances, additional oxygen may be required,[22] in addition to intravenous (IV) fluids.[25] Mechanical ventilation may also be required in severe cases.[35]

In Ireland, there are currently no antivirals authorised for the treatment of lower respiratory tract infection (LRTI) caused by RSV. While ribavirin has been used internationally for the treatment of RSV in certain infant and adult populations considered at high risk of lower respiratory tract disease,[6] routine use in previously healthy individuals is not recommended due to limited evidence of clinical effectiveness,[36, 37] high cost, and potential adverse effects (including teratogenicity).[6, 38] It should be noted that on 22 June 2021, the marketing

authorisation for ribavirin was withdrawn for commercial reasons, and therefore it is no longer authorised for use in Ireland[39] or the EU.[40]

2.5 Prevention of RSV and immunoprophylaxis

2.5.1 Strategies for prevention of RSV in Ireland

Given that there is no specific therapy licensed to treat RSV, the mainstay of management focuses on infection prevention and supportive therapy.[6] The effectiveness of prevention strategies in minimising virus transmission were demonstrated during the COVID-19 pandemic, when such strategies were extremely effective, not only in minimising the case of SARS-CoV-2 transmission, but also for other respiratory viruses, including RSV.[6]

To reduce transmission of RSV, measures such as maintaining good hand hygiene are encouraged, and those who suspect they may have RSV are advised to isolate at home if they are symptomatic or feel unwell.[24] Individuals who are experiencing respiratory symptoms are encouraged to maintain good respiratory hygiene practices, such as covering their mouth and nose with a tissue when coughing or sneezing. Individuals who present with respiratory symptoms, or who have been in close contact with an individual infected with RSV, should avoid close contact with individuals who may be more at risk of severe disease caused by viral infection (such as young infants, older adults, and individuals who are immunocompromised). Particular care should be taken in seasonal periods to limit exposure of these vulnerable groups to the virus. As viral droplets can survive on hard surfaces for a number of hours, care should be taken within the home to ensure that surfaces such as doorknobs and countertops are disinfected, and ensuring that members of the household do not share cups, plates, glasses or utensils.[22]

In a hospital setting, additional preventative measures could include avoiding overcrowding on wards, managing RSV-positive patients in the same ward, ensuring that staff wear barrier clothing such as disposable gown and gloves when caring for infected patients, and restricting visiting where necessary.[22]

2.5.2 Immunoprophylaxis for prevention of severe RSV disease

As noted in Chapter 1, the potential to reduce morbidity and mortality associated with RSV improved with the authorisation of new products which provide both passive and active immunisation against RSV. These include a long-acting monoclonal antibody (authorised in Europe/EEA in October 2022), and two vaccines (authorised in Europe/EEA in June and August 2023). These products, and populations in whom their use is authorised, are described in detail below. In addition, palivizumab, a short-acting monoclonal antibody which is the only form of

immunoprophylaxis against RSV for which funding is provided in Ireland at present, is also described. A summary of the key characteristics of the products available can be seen in Table 2.1.

Palivizumab (Synagis®), manufactured by AstraZeneca, is a recombinant humanised monoclonal antibody produced in mouse myeloma host cells. It received marketing authorisation from the European Medicines Agency (EMA) in 1999. It may be administered directly to neonates and infants aged two years or less who are at high risk of serious lower respiratory tract disease caused by RSV (see Table 2.1 for licensed therapeutic indications). It is available in one pharmaceutical form, a single-dose vial containing powder for reconstitution and accompanying solvent, which is made up to either 0.5ml or 1ml of solution for injection (100mg/ml). Palivizumab is a short-acting monoclonal antibody, and is administered once a month for the duration of the RSV season, until the risk of infection with RSV has subsided. Where possible, the first dose should be administered prior to the commencement of the RSV season. Palivizumab attaches to the 'A' antigenic site of the 'F protein' which is located on the RSV cell surface. This prevents the virus from entering the human host cells, thereby preventing infection and viral replication and reducing the risk of RSV-related lower respiratory tract disease. To reduce risk of rehospitalisation, it is recommended that children receiving palivizumab, who become hospitalised with RSV, continue to receive monthly doses for the duration of the RSV season.[7]

Nirsevimab (Beyfortus®), manufactured by AstraZeneca and commercialised by Sanofi Winthrop,[41] is a recombinant human immunoglobulin monoclonal antibody produced in Chinese hamster ovary cells.[8] It received marketing authorisation from the EMA in October 2022. It is indicated for neonates and infants during their first RSV season for prevention of lower respiratory tract disease caused by RSV. As such, it should be administered from birth in the case of neonates born during their first RSV season, and prior to commencement of the RSV season for those entering their first RSV season. It is available in one pharmaceutical form, a pre-filled syringe containing either 0.5ml or 1ml of solution for injection (100mg/ml). Nirsevimab is a long-acting monoclonal antibody which typically needs to only be administered once during an RSV season. Like palivizumab, it is administered directly to neonates and infants. Nirsevimab provides passive immunity against RSV disease by attaching to the 'F protein' which is located on the RSV cell surface. As in the case of palivizumab, when the monoclonal antibody attaches to this surface protein, the virus is unable to enter the human body cells, and so cannot replicate. In this way, nirsevimab helps to prevent infection with RSV, thereby reducing the risk of RSV disease.[8]

RSVpreF (Abrysvo®), manufactured by Pfizer Europe MA EEIG, is a recombinant bivalent vaccine produced in Chinese hamster ovary cells. It received marketing

authorisation from the EMA in August 2023. RSVpreF is administered as a single dose and is indicated to provide passive protection against lower respiratory tract disease (LRTD) caused by RSV in infants from birth through six months of age following maternal immunisation of pregnant women (between 24 and 36 weeks gestation), and for the active immunisation of adults aged 60 years and older. It is available in one pharmaceutical form, a single dose vial containing powder for reconstitution, with accompanying solvent issued in a pre-filled syringe. RSVpreF contains two recombinant stabilised RSV prefusion F antigens, which represent both RSV-A and RSV-B subgroups. When the vaccine is administered, these prefusion F antigens elicit an immune response, resulting in production of RSV neutralising antibodies which protect against RSV-associated LRTD. Transplacental transfer of these antibodies confers passive immunisation to the infants born to vaccinated mothers.[9]

RSVPreF3 (Arexvy®), manufactured by GlaxoSmithKline Biologicals S.A., is a recombinant adjuvanted vaccine which is also produced in Chinese hamster ovary cells, and received marketing authorisation from the EMA in June 2023. RSVPreF3 is administered as a single dose, and is indicated in adults aged 60 years and older for active immunisation and prevention of lower respiratory tract disease caused by RSV. It is available in one pharmaceutical form, a single-dose vial containing powder for reconstitution, with accompanying suspension in an additional single-dose vial. RSVPreF3 is a monovalent vaccine, but has demonstrated comparable efficacy against both RSV A and RSV B subtypes.[42] RSVPreF3 combines the RSV-specific prefusion 'F protein', with an adjuvant system ($AS01_E$). The 'F protein' antigen elicits an immune response in the vaccinated individual, resulting in production of neutralising antibodies. The adjuvant system also facilitates the generation of RSVPreF3-specific CD4+ T cells. If the vaccinated individual is exposed to RSV, both the neutralising antibodies and T cells are reactivated, and this immune response should provide protection against lower respiratory tract disease caused by the virus.[10]

For all products, it is important to ensure that individuals do not have hypersensitivity to either the active substances or any excipients.[7-10]

While all medicines are monitored after EU market authorisation has been granted, some medicines are monitored more closely than others.[43] The EMA publishes a list of medicines for which additional monitoring is required,[44] which is reviewed monthly by the Pharmacovigilance Risk Assessment Committee (PRAC).[43] This list specifies the reason for which additional monitoring is required,[44] and medicines which are published on this list are distinguished by a black inverted triangle and accompanying warning displayed on both the Summary of Product Characteristics (SmPC) and package leaflet.[45] Additional monitoring will always apply in the case of

medicines which have been authorised in the EU after 1 January 2011, and contain either a new active substance, or where the medicine is a new biological medicine (for example, a vaccine).[43] Nirsevimab, RSVpreF and RSVPreF3 were added to the EMA's list of medicines under additional monitoring within a month of receiving market authorisation, and remain on the list as of May 2024.[44] Medicines may remain under additional monitoring for five years, or until the PRAC decides to remove them from the list.[43]

Table 2.1 Summary of the key characteristics of medicinal products authorised for immunisation against respiratory syncytial virus, as of 1 July 2024.

Trade name	Synagis®[7]	Beyfortus®[8]	Abrysvo®[9]	Arexvy®[10]
Active substance	Palivizumab (monoclonal antibody)	Nirsevimab (long-acting monoclonal antibody)	RSVpreF (recombinant, bivalent vaccine)	RSVPreF3 (recombinant, adjuvanted vaccine)
Marketing authorisation holder	AstraZeneca AB	Sanofi Winthrop Industrie*	Pfizer Europe MA EEIG	GlaxoSmithKline Biologicals S.A.
EMA marketing authorisation	13 August 1999	31 October 2022	23 August 2023	06 June 2023
Vaccination schedule	▪ 15mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. ▪ Palivizumab is given once a month during the RSV season. ▪ If possible, the first dose should be given before the season starts. Patients generally receive up to a total of five monthly injections into the thigh muscle.	▪ Infants with body weight <5kg: Single dose of 50mg (0.5ml)~ ▪ Infants with body weight ≥5kg: Single dose of 100mg (1ml). ▪ Nirsevimab should be administered prior to commencement of the RSV season, or from birth for infants born during the RSV season.^	▪ Pregnant women: Single dose of 0.5ml to be administered between weeks 24 and 36 of gestation. ▪ Adults aged 60 years and older: Single dose of 0.5ml.	▪ Adults aged 60 years and older: Single dose of 0.5ml.
Formulation	Each dose contains either: ▪ 50mg of palivizumab[1] in 0.5ml (100mg/ml); or ▪ 100mg of palivizumab[1] in 1ml (100mg/ml). [1]Recombinant humanised monoclonal antibody produced by DNA technology in mouse myeloma host cells.	Pre-filled syringe containing either: ▪ 50mg of nirsevimab[1] in 0.5ml (100mg/ml); or ▪ 100mg of nirsevimab[1] in 1ml (100mg/ml). [1]Human immunoglobulin G1 kappa monoclonal antibody produced in Chinese hamster	After reconstitution, one dose (0.5ml) contains: ▪ RSV subgroup A stabilised prefusion F antigen[1,2], 60mcg ▪ RSV subgroup B stabilised prefusion F antigen[1,2], 60mcg. [1]Glycoprotein F stabilised in the prefusion conformation.	After reconstitution, one dose (0.5ml) contains: ▪ RSVPreF3[1] antigen[2,3], 120mcg. [1]RSVPreF3 – RSV recombinant glycoprotein F stabilised in the prefusion conformation. [2]RSVPreF3 produced in Chinese hamster ovary cells by recombinant DNA technology.

		ovary cells by recombinant DNA technology.	[2]Produced in Chinese hamster ovary cells by recombinant DNA technology.	[3]Adjuvanted with $AS01_E$ containing: ▪ plant extract *Quillaja saponaria* Molina, fraction 21, 25mcg ▪ 3-O-desacyl-4'-monophosphoryl lipid A from *Salmonella mennesota*, 25mcg.
Therapeutic Indications	Indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by RSV in children at high risk for RSV disease: ▪ Children born at 35 weeks of gestation or those aged less than 6 months at the onset of the RSV season. ▪ Children less than two years of age and requiring treatment for bronchopulmonary dysplasia within the last six months. ▪ Children less than two years of age with haemodynamically significant congenital heart disease.	Indicated for the prevention of lower respiratory tract disease caused by RSV in neonates and infants during their first RSV season.	Indicated for: ▪ Passive protection against lower respiratory tract disease caused by RSV in infants from birth through to 6 months of age following maternal immunisation through pregnancy. ▪ Active immunisation of adults aged 60 years and older for the prevention of lower respiratory tract disease caused by RSV.	Indicated for active immunisation of adults aged 60 years and older for the prevention of lower respiratory tract disease caused by RSV.
Subject to additional monitoring requirements by the EMA	No.[44]	Since November 2022, nirsevimab has been subject to additional monitoring by the EMA, owing to the fact that it is a new active substance and new biological medicine.[44]	Since September 2023, RSVpreF has been subject to additional monitoring owing to the fact that it is a new active substance and new biological medicine.[44]	Since June 2023, RSVPreF3 has been subject to additional monitoring by the EMA, owing to the fact that it is a new active substance and new biological medicine.[44]

Key: DNA – deoxyribonucleic acid; EMA – European Medicines Agency; RSV – respiratory syncytial virus.
*AstraZeneca AB led on development, and are responsible for the manufacture of nirsevimab (Beyfortus®). Sanofi Winthrop Industrie are responsible for marketing activities and commercialisation of nirsevimab, and, as such, hold the marketing authorisation for nirsevimab in Europe.[8, 41]
~For infants undergoing cardiac surgery with cardiopulmonary bypass, an additional dose may be administered as soon as the infant is stable after surgery to ensure adequate nirsevimab serum levels.

^In July 2023, the EMA's Committee for Medicinal Products for Human Use (CHMP) discussed the extension of indication of nirsevimab to include treatment of children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[46] This was based on interim results presented by AstraZeneca AB, from studies D5290C00005 and D5290C00008.[46] Supplementary information was requested by the CHMP from AstraZeneca AB in July 2023,[46] with further requests for supplementary information made in October 2023 to AstraZeneca AB,[47] and in January 2024 to Sanofi Winthrop Industrie.[48] On 27 June 2024, the EMA's CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for nirsevimab (Beyfortus®) to include children aged up to 24 months who remain vulnerable to severe RSV disease through their second RSV season.[49]

2.5.3 Co-administration with other vaccines

Palivizumab and nirsevimab are monoclonal antibodies specific for RSV, thus neither are expected to interfere with the immune response of any co-administered vaccines.[7, 8] The European Public Assessment Report (EPAR) for palivizumab specifies that no formal interaction studies with other medicinal products have been conducted. However, it notes that in the phase III IMpactRSV study in the premature and bronchopulmonary dysplasia paediatric populations, the proportions of patients in both placebo and palivizumab groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar, and no incremental increase in adverse reactions was observed among patients receiving these agents.[7] The EPAR for nirsevimab specifies that it can be given with childhood vaccines,[8] and states that in clinical trials, when nirsevimab was given with routine childhood vaccines, that the safety and reactogenicity profile of the co-administered regimen was similar to when the childhood vaccines were given alone.[8] However, the EPAR notes that there is limited experience of co-administration of nirsevimab with other vaccines.[8]

RSVpreF may be co-administered with the seasonal quadrivalent influenza vaccine (QIV, surface antigen, inactivated, adjuvanted).[9] However, the EPAR for RSVpreF highlights that, in a randomised study conducted in adults aged 65 years and older, numerically lower RSV A and RSV B neutralising titres and numerically lower influenza A and B haemagglutination titres were observed when RSVpreF and an inactivated adjuvanted seasonal influenza vaccine were co-administered than when they were given separately.[9] The clinical significance of this is unknown, and a criterion for non-inferiority of the immune responses in the co-administration versus the separate information group was considered to be met.[9] A minimum interval of two weeks is recommended between administration of RSVpreF and administration of a tetanus, diphtheria and acellular pertussis vaccine (Tdap). No safety concerns were identified when RSVpreF was co-administered with Tdap in healthy non-pregnant women.[9] Immune responses to RSV A, RSV B, diphtheria and tetanus on co-administration were non-inferior to those after separate administration. The EPAR for RSVpreF highlights that the immune responses to the pertussis components were lower on co-administration compared with separate administration, and did not meet the criterion for non-inferiority. The clinical relevance of this finding is unknown.[9] The EPAR also notes that no formal interaction studies have been conducted to inform possible co-administration with other vaccines.[9]

RSVPreF3 may be co-administered with inactivated seasonal influenza vaccines, specifically standard dose unadjuvated, high-dose unadjuvanted, and standard dose adjuvanted vaccines.[50] The Summary of Product Characteristics (SmPC) highlights that when RSVPreF3 and seasonal influenza vaccines were administered

concomitantly, numerically lower RSV A and B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed compared to separate administration.[50] However, it is noted this was not observed consistently across studies and the clinical significance of these findings is not known.[50] Where RSVPreF3 is to be administered with another injectable vaccine at the same visit, the vaccines should always be administered at different injection sites.[10]

It should be noted that co-administration of either RSVpreF or RSVPreF3 with one or more vaccines at the same visit may increase local or systemic reactogenicity.[51]

2.5.4 Administration and manufacturers' stipulated storage

All four medicinal products (both monoclonal antibodies and vaccines) are to be administered by intramuscular injection.[7-10] Both monoclonal antibodies (palivizumab and nirsevimab) should be administered preferably in the anterolateral aspect of the thigh, with manufacturers specifying that the gluteal muscle should not be used routinely as an injection site, owing to potential risk of damage to the sciatic nerve.[7, 8] In the case of palivizumab, where injection volumes over 1ml are required, then these should be given as a divided dose.[7] Both vaccines (RSVpreF and RSVPreF3) should be administered in the deltoid muscle of the upper arm.[9, 10]

All four medicinal products (both monoclonal antibodies and vaccines) should be stored in a refrigerator at 2°C to 8°C.[7-10] None should be frozen,[7-10] and manufacturers for palivizumab, nirsevimab and RSVPreF3 specify that each should be stored in their original outer packaging to protect from light.[7, 8, 10] Nirsevimab should not be exposed to direct heat.[8] The manufacturers' instructions for both monoclonal antibodies (palivizumab and nirsevimab) specify that the products should not be shaken.[7, 8]

Palivizumab must be administered immediately after drawing the dose from the vial into the syringe.[7] After removal from the refrigerator, nirsevimab must be used within eight hours or discarded.[8] From a microbiological point of view, manufacturers advise that both RSVpreF and RSVPreF3 should be administered immediately after reconstitution;[9, 10] RSVpreF may be administered up to four hours following reconstitution if stored between 15°C and 30°C.[9] Similarly, RSVPreF3 may be administered within four hours following reconstitution if stored at 2°C to 8°C, or if stored at room temperature up to 25°C.[10] All products should be inspected visually prior to administration, and should not be administered if discolouration is found, or if large or foreign particulate matter is present.[7-10]

2.5.5 Dosing schedule

Both monoclonal antibodies (palivizumab and nirsevimab) are dosed based on infant body weight in kilograms (kg).[7, 8] Palivizumab is given at monthly intervals during the RSV season, with the first dose ideally administered before the RSV season commences. The recommended dose for infants is 15mg/kg of body weight.[7] Nirsevimab is typically given as a single dose per RSV season, which should be administered to infants either (i) before the RSV season commences or (ii) from birth where an infant is born during the RSV season. For infants with a body weight of less than 5kg, a single dose of 50mg is recommended and administered by pre-filled syringe (50mg/0.5ml). For infants with a body weight of 5kg or more, a single dose of 100mg is recommended, also administered by a pre-filled syringe (100mg/ml). An additional dose may be required for infants undergoing cardiac surgery with cardiopulmonary bypass to ensure adequate nirsevimab serum levels; this should be administered as soon as the infant is stable post-surgery. The dose depends on the time lapse since the first dose: if within 90 days, the additional dose is either 50mg or 100mg depending on bodyweight, as above. If more than 90 days have elapsed, a single dose of 50mg is recommended.[8]

In the case of both vaccines (RSVpreF and RSVPreF3), the dose for adults aged 60 years and older is 0.5ml.[9, 10] In the case of RSVpreF, the dose for pregnant women of between 24 and 36 weeks' gestation is also 0.5ml.[9]

2.5.6 NIAC recommendations regarding immunoprophylaxis against RSV in Ireland

The introduction of an infant immunisation programme has the potential to reduce morbidity and mortality associated with RSV, and reduce healthcare utilisation during the busy winter period.[11] Immunisation against RSV is not currently included as part of either the routine childhood or adult immunisation schedule in Ireland. In October 2023, the National Immunisation Advisory Committee (NIAC) recommended the passive immunisation of all infants against RSV during their first RSV season, and the vaccination of adults aged 65 years and older prior to the commencement of the RSV season.[11]

At present, palivizumab is the only form of immunoprophylaxis against RSV which is funded by the Health Service Executive (HSE) in any patient population. It is offered to neonates and infants aged two years of age or less who are considered at high risk of serious complications of lower respiratory tract disease caused by RSV,[7] as previously outlined in Table 2.1. NIAC has also recommended that, when available, nirsevimab should replace palivizumab for those high-risk infants and children who are currently eligible to receive palivizumab.[11]

Further details of NIAC recommendations regarding immunoprophylaxis against RSV in Ireland are outlined in Chapter 3.

2.6 Discussion

RSV is a highly transmissible respiratory infection.[22] In healthy adults and children, the majority of cases are self-limiting, with those infected typically experiencing mild respiratory or systemic symptoms which do not require medical attendance.[24] However, certain populations are at a higher risk of lower respiratory disease and complications, and may be more likely to suffer greater morbidity. These populations include infants, young children and older adults, and also those with compromised immune systems or with certain co-morbidities of the heart and lungs.[22]

Those at high risk of RSV infection may also experience greater levels of viral shedding, and for longer periods.[52] As such, transmissibility among those at high risk of RSV is more significant. This is of particular concern, as often those groups considered as high risk, such as infants, young children and older adults, or individuals who are frequently hospitalised, may be more likely than others to be in environments where contact patterns are amplified (for example, in organised childcare facilities, long-term residential care facilities or inpatient hospitalisation). In these types of environments, transmission of the virus may be more difficult to prevent, potentially increasing the risk of outbreaks and consequently the risk of exposure to the pathogen.

Given the seasonal nature of RSV transmission,[22] and the potential for co-infection with other respiratory diseases where immunity is reduced, the seasonal burden on healthcare systems can be substantial.[53, 54] While it is unclear whether co-infection results in increased morbidity for a patient,[32] it may prolong the period of illness experienced by the infected individual. Immunisation may reduce the risk of infection and transmission, and thus reduce the annual seasonal burden on healthcare providers through reduced healthcare utilisation.

Historically, only one product, the monoclonal antibody palivizumab (Synagis®) was available for the prevention of RSV, with its use limited to specific groups of infants at high risk of disease. Since 2022, two new products have been authorised for passive infant immunisation: a long-acting monoclonal antibody, nirsevimab (Beyfortus®), and a maternal vaccine, RSVpreF (Abrysvo®). RSVpreF is also authorised for active immunisation against RSV in adults aged 60 years and older, as is an additional vaccine, RSVPreF3 (Arexvy®), which has been authorised in Europe since June 2023. Multiple other RSV vaccines and monoclonal antibodies are in development,[55] and while not included in this assessment, it is noted that, on 27 June 2024, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for a new mRNA vaccine, mResvia, for the prevention of lower respiratory tract disease caused by RSV in adults aged 60 years and older.[56]

Immunisation methods targeting the highly conserved RSV 'F' membrane protein are advantageous, as there is minimal risk of antigenic drift occurring.[57] As such, vaccine or monoclonal antibody formulation can remain unchanged from one season to the next, without any expected reduction in effectiveness. This is in contrast to seasonal influenza vaccines which are strain-specific, which results in annual variations in their reported vaccine effectiveness. However, it should be noted that while the 'F protein' is highly conserved in both RSV-A and RSV-B strains, mutations can exist, though they are rare. Where mutations are present, the monoclonal antibodies may show lower binding affinity to the 'F protein' and so may be unable to neutralise the virus.[58] Viruses resistant to both nirsevimab[59] and palivizumab[60] have been identified.

In Ireland, immunisation against RSV is currently not included as part of either the childhood or adult immunisation programmes, with the exception of palivizumab for infants at high risk of severe disease. Since the authorisation of the long-acting monoclonal antibody (nirsevimab) and maternal vaccine (RSVpreF), NIAC has recommended passive immunisation of all infants in their first RSV season.[11] The prematurity of infant immune systems after birth renders even healthy infants more susceptible to lower respiratory tract disease as a result of RSV infection.[61] A universal infant immunisation programme would be expected to reduce the incidence of RSV in this age group, and consequently alleviate the burden on the healthcare system. NIAC do not currently indicate a preference for passive immunisation with a monoclonal antibody or maternal vaccination in the general infant population.[11]

NIAC has also recommended that, when available, nirsevimab should replace palivizumab for those high-risk infants and children who are currently eligible to receive palivizumab.[11] As highlighted in section 2.5.2, nirsevimab is a long-acting monoclonal antibody, with data suggesting that one dose will infer protection to the infant against RSV for up to six months after administration.[8] In contrast, palivizumab is a short-acting monoclonal antibody, and must be administered monthly, with typically up to five doses required.[7] If nirsevimab became the first-choice monoclonal antibody for immunoprophylaxis of high-risk infants against RSV, it would be expected that burden would be reduced for the infant, the infant's caregivers, and the healthcare system through reduced number of appointments required for product administration and potentially reduced risk of local reactogenic effects in infants as a consequence of reduced frequency of dosing. In addition, use of nirsevimab would eliminate any existing risk where dosing intervals between monthly palivizumab injections may extend beyond the optimal period, or where missed doses occur, ultimately ensuring that protection for the infant against RSV is at reduced risk of being compromised.

NIAC has also recommended RSV vaccination of adults aged 65 years and older, with vaccine administration recommended prior to commencement of the RSV season, where possible. NIAC does not currently indicate a preference for either RSVpreF or RSVPreF3, owing to the similar efficacy and safety profiles of both vaccines.[11] Immunosenscence, or the age-related decline of an individual's capacity to mount an immune response to either pathogens or vaccines, is a phenomenon that renders the older adult population at increased risk of morbidity and mortality associated with infectious diseases.[62] The addition of an RSV vaccine to the adult seasonal vaccination programme aims to reduce the burden of illness associated with RSV in older adults.

Until recently, interventions to reduce the burden of RSV were limited to palivizumab for infants at high risk of severe disease. Since 2022, several new preventive interventions have been authorised that aim to reduce the burden of RSV in the general infant and older adult populations. The costs of these alternative RSV immunisation strategies in infants and older adults are explored in Chapter 5.

3 Summary of international practice for immunisation of infants and older adults against respiratory syncytial virus (RSV)

Key Points

- A review of international practice was undertaken to identify recommendations and policy with respect to the immunisation of infants and older adults against respiratory syncytial virus (RSV) in EU/EEA countries and the UK.
- Data were identified for 31 countries, including Ireland, with this chapter providing a summary of current international practice, as of 1 July 2024. The key points below relate to the countries for which information was identified, with a focus on where immunisation is currently offered, or planned to be offered, and whether it is publicly funded. Of note, nirsevimab and the RSV vaccines are not as yet marketed in all examined countries.
- In Ireland, immunisation against RSV is recommended by the National Immunisation Advisory Committee (NIAC) for all infants in their first RSV season and for adults aged 65 years or older. Palivizumab is currently funded for infants at high risk of RSV-associated disease, but NIAC recommends that palivizumab is repaced by nirsevimab for this cohort. A publicly-funded pilot (Pathfinder) that offers immunisation with nirsevimab is being implemented for all infants born during the 2024-2025 RSV season. For older adults, currently no RSV immunisation programme is in place, or planned, for the 2024-2025 RSV season.
- Across the other 30 EU/EEA and UK countries, where information was identified regarding the passive immunisation of infants in the general population with nirsevimab and or the maternal vaccine, immunisation is consistently recommended by the relevant National Immunisation Technical Advisory Group (NITAG) or HTA body, but not necessarily funded by the relevant Ministry for Health or equivalent body.
- For the general infant population, five countries (Belgium, France, Germany, Spain and the UK) have publicly-funded immunisation programmes planned or in place for the 2024-2025 RSV season. All five countries will fund immunisation for all infants entering their first RSV season, irrespective of whether they were born during or outside of the RSV season. The programmes vary in terms of the method of immunisation (that is, use of nirsevimab and or the maternal vaccine), eligibility (in terms of the gestational window for the maternal vaccine), the periods during which immunisation can be accessed

(defined period or year-round), and priority groups for immunisation (for example, in the event of limited supply).

  - The UK will offer the maternal vaccine (from 28 weeks gestation until delivery) on a year-round basis from 1 September 2024.
  - In Spain and Germany, nirsevimab will be offered in the weeks prior to and during the RSV season (October to March).
  - In Belgium and France, a choice of the maternal vaccine or nirsevimab will be offered. In cases where the pregnant woman receives the maternal vaccine less than two weeks before birth, the infant will also be eligible to receive nirsevimab.
    - In Belgium, pregnant women (expected to deliver between September and March, inclusive) will be offered the maternal vaccine from 28 to 36 weeks' gestation. Nirsevimab will be offered in the weeks prior to and during the RSV season (October to March).
    - In France, the vaccine will be offered to women between 32 to 36 weeks' gestation during the same window when nirsevimab is being offered (September to January).

- For the passive immunisation of infants at increased risk of RSV disease, immunisation is widely recommended, but not necessarily funded. Until 2023, these recommendations were limited to palivizumab. Prior to the adoption of nirsevimab by five countries, the provision of palivizumab to those at increased risk of RSV disease was funded (fully or partially) in 18 countries and also in Ireland. Of the five countries (Belgium, France, Germany, Spain and the UK) with publicly-funded immunisation programmes planned or in place for the 2024-2025 RSV season:
  - Four countries (Belgium, France, Germany and Spain) preferentially recommend nirsevimab in place of palivizumab for infants and children at increased risk of RSV disease.
  - In the UK, infants and children at increased risk of RSV disease will be offered passive immunisation with palivizumab, regardless of whether the mother was vaccinated during pregnancy.
- For the prevention of RSV-associated disease in older adults, only the UK was identified as planning to implement a publicly-funded programme offering once-off vaccination for all adults aged 75 to 79 years from September 2024. In the Czech Republic, while RSV vaccines are available on an individual basis

for adults aged 60 years or older and are partially funded through insurance, they are not part of an immunisation programme.

- For five of the countries identified to have publicly-funded RSV immunisation programmes (for infants and or adults) planned or in place for the 2024-2025 RSV season, two countries (Belgium and Spain) have specified that their outlined approach to immunisation is for a single season with the intention to review their immunisation strategy for subsequent seasons. For the three other countries (France, Germany, and the UK), the outlined approach is not noted to be time-limited, although all three highlight that the programmes may be updated in line with the latest evidence.
- National recommendations in the countries examined were informed by the national and international epidemiology and burden of RSV and the rapidly evolving evidence in relation to each form of immunisation.
    - For nirsevimab, recommendations have been informed by evidence of efficacy and safety from five randomised controlled trials (RCTs) in addition to preliminary surveillance data from countries that implemented a programme of immunisation with nirsevimab during the 2023-2024 RSV season (namely Spain, Luxembourg and the US).
    - For the maternal vaccine, countries that have conducted assessments have primarily considered evidence from one RCT (MATISSE).
    - National recommendations on RSV vaccination for older adults were primarily informed by the results of five clinical trials: two related to RSVPreF3 (Arexvy®) and three related to RSVpreF (Abrysvo®). Further data provided by manufacturers informed recommendations in the US, which in turn informed recommendations in both Ireland and Sweden.
    - Published trial data for nirsevimab, the maternal vaccine and RSV vaccines for older adults that supported recommendations in the countries included in the review suggest that these agents are safe and effective. Moreover, early evidence of real-world safety and effectiveness of nirsevimab from countries that implemented immunisation for infants in the 2023-2024 season are broadly consistent with these trial data.
- International practice with respect to immunisation of infants and older adults against RSV is a rapidly changing area. It is likely that there will be updates to national practices for the 2024-2025 RSV season and subsequent seasons, as further evidence becomes available.

3.1 Introduction

The purpose of this chapter is to summarise the current international practice with respect to the immunisation of infants and older adults against respiratory syncytial virus (RSV) in EU/EEA countries and the UK. As described in Chapter 2, palivizumab is a monoclonal antibody, authorised by the European Medicines Agency (EMA) in August 1999 for the prevention of RSV-related serious lower respiratory tract disease in selected infants at high risk of RSV disease.[7] Recently, two additional forms of immunisation against RSV in infants have also been authorised. The first, nirsevimab,[8] was authorised in October 2022, and the second, Abrysvo® (referred to in the context of maternal vaccination as the maternal vaccine throughout this chapter),[9] was authorised by the EMA in August 2023. As of 1 July 2024, there were two vaccines authorised by the EMA for the prevention of lower respiratory tract infection (LRTI) caused by RSV in adults aged 60 years and older. RSVPreF3 (Arexvy®)[10] received EMA authorisation in June 2023 and RSVpreF (Abrysvo®)[9] received EMA authorisation in August 2023.

This chapter summarises the recommendations for the use of these monoclonal antibodies and vaccines in EU/EEA countries and the UK. Also summarised are details that could be identified in relation to their implementation and funding, as well as the evidence that informed decision-making. Throughout this chapter, implementation details primarily relate to the implementation of these monoclonal antibodies and vaccines as part of immunisation programmes — that is, as part of childhood or adult immunisation schedules or other types of immunisation programmes (such as pilot programmes or programmes limited to a single RSV season).

3.2 Methods

3.2.1 Research question

This review aimed to address the following research question:

- What practices do international or national organisations, agencies, guidelines, recommendations or position papers specify for the immunisation of infants and older adults against RSV?

The Population, area of Interest and Context (PICo) framework that was developed to address the research question is outlined in Table 3.1. For the purpose of this chapter, the umbrella term 'guidance documents' is used to describe the heterogeneous collection of guidelines, position papers, recommendations and policies identified for inclusion in this summary.

Table 3.1 PICo for literature review of international practice

Population	▪ Neonates and infants aged less than two years ▪ Pregnant women between 24 and 36 weeks' gestation ▪ Adults aged 60 years and older.
Interest	Practice, recommendations or guidelines for the immunisation of infants against RSV including: ▪ administration of antibody prophylaxis against RSV directly to neonates and infants using an EMA authorised monoclonal antibody ▪ administration of an EMA authorised maternal vaccine to pregnant women between 24 and 36 weeks' gestation ▪ administration of an EMA authorised RSV vaccine to adults aged 60 years and older.
Context	Guidance documents: ▪ guidelines (international, national) ▪ position papers ▪ recommendations ▪ implementation advice documents.

3.2.2 Search strategy

A systematic search was conducted using the PubMed Clinical Queries Tool on 18 December 2023. The search was restricted to between 1 January 2022 and 18 December 2023. There were no language restrictions. This was supplemented by a grey literature search of the following sources conducted on 11 March 2024: International HTA Database, the Global National Immunization Technical Advisory Groups (NITAGs) Network and Google Scholar. In addition, the websites of HTA agencies, ministries of health and public health agencies in EU/EEA countries and the UK were searched during March and April 2024. Searches of these websites were repeated on 2 July 2024 to confirm that the identified information was correct as of 1 July 2024 and or to identify any relevant updates in international practice, as appropriate.

3.2.3 Selection of studies and data extraction

Documents were assessed against the criteria outlined in Table 3.1. Google Translate was used to obtain translations of non-English documents.

3.3 Summary of international practice for the immunisation of infants

A brief overview of approaches to the immunisation of infants against RSV is provided in Table 3.2, with more detailed summaries provided in Appendix 3A Table 1. This section summarises the recommendations of EU/EEA countries and the UK with respect to the use of palivizumab, nirsevimab and the maternal vaccine as preventive measures against RSV infection in infants. Additionally, where available, information regarding funding of these preventive measures and their implementation as part of an immunisation programme has been summarised.

3.3.1 Palivizumab prophylaxis for the prevention of RSV in infants

Information regarding palivizumab prophylaxis was gathered, initially, from a 2022 systematic review of European Clinical Practice Guidelines (CPGs) for RSV prophylaxis. The 2022 systematic review was conducted by the REspiratory Syncytial virus Consortium in Europe (RESCEU).[63] It identified 20 national CPGs (from 20 countries) on RSV prophylaxis published between 2000 and 2018. The systematic review authors checked for updates to included CPGs between February 2020 and January 2022. Funding practices for the included countries were outside the scope of the 2022 review, so the recommendations summarised below may not reflect funding policy. In addition to the 20 countries[1] for which CPGs were identified, the systematic review authors received confirmation that Denmark and Belgium had CPGs under development at the time of the review, whereas Iceland and Finland had no national CPGs for RSV prophylaxis.

Recommendations from the 20 countries regarding the use of palivizumab for RSV prophylaxis in infants at high risk of RSV disease, as reported in the 2022 systematic review, are summarised below:

- all included countries recommended the use of palivizumab or that it should be considered for infants with bronchopulmonary dysplasia (BPD)
    - the age cut-off for eligibility for infants with BPD differed across countries, with 14 countries including infants aged less than 24 months, five countries including infants aged less than 12 months, and one country including infants aged less than nine months

[1] Austria, Bosnia and Herzegovina, Czech Republic, France, Germany, Greece, Italy, Ireland, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK.

- 17 countries recommended the use of palivizumab or that it should be considered for infants with congenital heart disease (CHD)
    - the age cut-off for eligibility for infants with CHD differed across countries, with 11 countries including infants aged less than 24 months, five countries including infants aged less than 12 months, and one country including infants aged less than six months
- 12 countries recommended the use of palivizumab or that it should be considered for children with severe combined immunodeficiency (SCID)
    - the age cut-off for eligibility for infants with SCID varied, with seven countries including infants aged less than 24 months, three countries including infants aged less than 12 months, and two countries not stating the age cut-off.

Recommendations for infants born prematurely differed across the 20 included countries, specifically in relation to gestational age cut-off:

- A total of 19 countries had recommendations regarding the use of palivizumab in infants born prematurely. For infants born extremely prematurely (that is, less than 29 weeks' gestational age (wGA), or less than 26 wGA in Sweden), 15 of the 19 countries recommended palivizumab or that its use should be considered. Four of the 19 countries only recommended its use (or consideration of its use) if additional risk factors were present, such as comorbidity, being in childcare, or having older siblings. One country (Switzerland) did not recommend palivizumab in premature infants.
    - A total of 10 countries had an age cut-off for eligibility for these infants of less than 12 months old. Four countries restricted the age cut-off to less than nine months old and four countries to less than six months old. One country restricted the age cut-off to less than three months old.
- For infants born between 29 wGA and 32 wGA, six countries recommended palivizumab or that its use should be considered. A further 11 countries did so only if additional risk factors (as above) were present. One country (Austria) recommended palivizumab following an RSV risk score assessment.
    - A total of 13 countries had an age cut-off for eligibility of less than six months old; two countries had an age cut-off of less than 12 months old, while three restricted the age cut-off to less than three months old.
- For infants born between 32 wGA and 35 wGA, 10 countries recommended palivizumab or that its use should be considered if additional risk factors (as above) were present.

  - A total of six countries had an age cut-off for eligibility of less than six months old; one restricted the age cut-off to less than three months old, one to less than 10 weeks and two countries to less than 1.5 months.

To inform this chapter, the HIQA evaluation team supplemented the findings from the RESCEU 2022 systematic review with additional information identified through a bespoke search strategy relating to palivizumab prophylaxis, specifically:

- information for EU/EEA and UK countries not included in the systematic review
- any updated information identified for the countries included in the systematic review
- funding information (as funding policies were outside the scope of the 2022 systematic review)
- findings from the European Foundation for the Care of Newborn Infants (ECFNI) 2021 position paper on RSV in preterm and ill infants.
- expert opinion feedback from members of the Expert Advisory Group.

The following additional information was identified:

- in Iceland, palivizumab is available on prescription as an 'exempt medicine' (that is, it has marketing authorisation, but is not marketed in that country).
- an additional 11 countries recommend palivizumab prophylaxis against RSV for children at high risk of disease (see Table 3.2)
  - in three of these countries (Belgium, Bulgaria, Croatia), palivizumab is administered as part of an immunisation programme
  - for the other eight countries (Cyprus, Denmark, Estonia, Finland, Hungary, Liechtenstein, Lithuania, Luxembourg), either it is not part of a formal immunisation programme, or information was not identified with respect to its inclusion in an immunisation programme
  - palivizumab prophylaxis is eligible for funding in seven of these countries (Belgium, Bulgaria, Croatia, Hungary, Liechtenstein, Luxembourg, and Romania).
- prior to the availability of nirsevimab and the maternal vaccine, palivizumab was funded (fully or partially) in 18 countries and also in Ireland for those at increased risk of RSV disease.
- As will be outlined in section 3.3.2 below, countries are in the process of updating their RSV immunisation policy recommendations. Of the five countries identified to have updated their RSV immunisation programmes to provide publicly-funded nirsevimab and or the maternal vaccine for the 2024-2025 RSV season:

- four (Belgium, France, Germany and Spain) preferentially recommend nirsevimab in place of palivizumab for children at increased risk of RSV disease
- in the UK, infants at increased risk of RSV disease will be offered passive immunisation with palivizumab, regardless of whether the mother was vaccinated during pregnancy.

Table 3.2 outlines whether or not palivizumab is recommended, available, funded, and or part of an immunisation programme for each of the 31 countries included in the current review. Detailed information on each country's recommendations relating to RSV prophylaxis with palivizumab are provided in Appendix 3A Table 1.

3.3.2 Recommendations on the use of nirsevimab or the maternal vaccine for the prevention of RSV in infants

The search (see section 3.2.2) with respect to EU/EEA countries and the UK identified 18 countries, including Ireland, with published information relating to the use of nirsevimab and or the maternal vaccine for the prevention of RSV in infants. A brief summary of the 11 countries for which this information included recommendations, information on funding and implementation as part of an immunisation programme, and or the evidence underpinning any recommendations made is provided below. An overview of the information identified for all countries is provided in Table 3.2. More detailed summaries for each country and additional details regarding eligible cohorts for a given recommendation are outlined in Appendix 3A Table 1. Summaries of the clinical trials listed as being used to inform recommendations are provided in section 3.3.3.

Austria

According to the Austrian Vaccination Plan 2023-2024, published in September 2023, nirsevimab is approved for the prevention of RSV disease in newborns, infants and young children during their first RSV season. Nirsevimab is expected to be launched on the market in Austria during 2024, and will not be available free of charge.[64] It also states that the maternal vaccine has been available in Austria since autumn 2023 and pregnant women can avail of this vaccine on an individual basis, preferably between September and March. The maternal vaccine is not available free of charge.[64]

While the evidence base underpinning the recommendations is not explicitly stated, the Austrian Vaccination Plan 2023-2024 includes a summary of international literature that highlights the significant disease burden experienced by children as a result of RSV infection, including acute LRTIs, hospitalisations and mortality in children aged under five years.

Belgium

In December 2023, the Superior Health Council (SHC) of Belgium published an advisory report providing temporary recommendations on the use of preventive measures against RSV disease.[65] The SHC noted that these recommendations will be updated in the future, as more evidence becomes available.

For the 2024-2025 RSV season, the SHC recommends, on a temporary basis, the use of:

- nirsevimab for all babies born to unvaccinated mothers or within two weeks following administration of the maternal vaccine, and for babies born prematurely (less than 30 wGA)
    - to be administered to those born during the RSV season (that is, from October to March)
    - to be administered to those aged six months or younger at the start of the RSV season (that is, those born from April to September)
- nirsevimab as a replacement for palivizumab for children classified as being at high risk of severe disease:
    - during their first RSV season, nirsevimab is recommended for children at high risk aged 11 months or younger and whose mother has either not been vaccinated or has been vaccinated at the end of the RSV season (January to March 2025)
    - during their second RSV season, nirsevimab is recommended for children at high risk, regardless of the vaccination status of the mother.
- the maternal vaccine for women expected to deliver between early September 2024 and end of March 2025 (administered between 28 and 36 wGA).

The maternal vaccine was made available in Belgium as of 10 January 2024 at a cost of €185.10 which is not funded and so must be paid for privately by individuals.[66] As of 1 June 2024, nirsevimab is funded for infants aged less than one year, with a co-payment of between €8 and €12.10 required by individuals when purchasing in pharmacies. However, nirsevimab is not expected to be available on the market in Belgium until September 2024.[67]

These recommendations were informed by considering the national and international epidemiology and burden of RSV infection, provided by Sciensano, and rapid reviews of the clinical efficacy and safety of nirsevimab and the maternal vaccine, provided by the Belgian Knowledge Exchange and Care Centre (KCE). The rapid reviews synthesised findings from pivotal clinical trials (see section 3.4) involving nirsevimab (D5290C00003, MELODY, MEDLEY, and HARMONIE) and the maternal vaccine

(MATISSE); the certainty of the evidence was ascertained using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The SHC noted that their advice aligns with that of the Advisory Committee on Immunization Practices (ACIP) in the US and the Joint Committee on Vaccination and Immunisation (JCVI) in the UK.

As noted in Chapter 2, in October 2022, nirsevimab received EMA marketing authorisation for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.[8] On 27 June 2024, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a change to the terms of the marketing authorisation for nirsevimab (Beyfortus®) to include children aged up to 24 months who remain vulnerable to severe RSV disease through their second RSV season.[49] The decision was informed by interim results from the MEDLEY and MUSIC trials.[47]

France

For the 2023-2024 season, nirsevimab was fully funded by the state without cost to the individual,[68] and was offered to those born during the RSV season (that is, from September until the end of January, for mainland France) and for infants born since 6 February 2023.[68] For the 2024-2025 RSV season, nirsevimab will be partially funded at a reimbursement rate of 30%.[69] Nirsevimab is available to all infants entering their first RSV season and as an alternative to palivizumab for eligible populations. In addition, in June 2024, Haute Autorité de Santé (HAS) updated the recommendation for the 2024-2025 RSV season to also include maternal vaccination with RSVpreF, administered between 32 and 36 weeks.[70] HAS recommends the 2024-2025 vaccination campaign either runs concomitant with the nirsevimab immunisation campaign, or begins in September and runs until the end of January. HAS recommends that the two strategies for immunisation of infants against RSV infections (that is, administration of nirsevimab to infants or vaccination of pregnant women with RSVpreF) be explained and offered to parents during pregnancy, so that they can make an informed decision between them.

In July 2023, the Transparency Committee of the HAS published an evaluation of nirsevimab. This evaluation considered the epidemiology and burden of RSV infection in infants in France, the need for preventive measures against RSV infection, and the clinical efficacy and safety results from clinical trials involving nirsevimab (D5290C00003, MELODY, MEDLEY, and HARMONIE). Aspects the Transparency Committee considered to support the use of nirsevimab included the considerable impact on healthcare services of RSV in infants at high risk of disease and the current inadequately met medical need for preventing RSV-associated LRTI during an infant's first RSV season.[71] In addition, the Committee noted the absence

of alternative therapeutics for preventing RSV in infants at low risk of severe disease. The Committee also noted evidence from clinical trials of the efficacy of nirsevimab compared with placebo on the reduction of medically-attended RSV-associated LRTI in infants at low risk of serious disease, and evidence that the safety profile of nirsevimab appears acceptable. Concerns identified regarding the evidence base for nirsevimab included the absence of clinical trial evidence directly comparing nirsevimab against palivizumab in infants at high risk of disease, and lack of data on the impacts of nirsevimab on lengths of hospital stay, admissions to intensive care units and mortality. With respect to the infants at high risk of disease, it noted that a single injection of nirsevimab is likely to be a more favourable experience for the patient compared with multiple injections of palivizumab.

In June 2024, HAS published an evaluation of the vaccination of pregnant women with the RSVpreF vaccine for preventing RSV infections in infants.[70] This evaluation considered the epidemiology and burden of RSV infection in infants in France, the available data from the 2023-2024 RSV season's immunisation campaign for infants with nirsevimab, and the clinical efficacy and safety results from clinical trials (C3671001, the SAVVY study, C3671004, the MATISSE study, C3671014, and WI257521). HAS also considered data relating to international recommendations from other countries relating to immunisation of infants against RSV, economic evaluations of maternal vaccination against RSV, and the acceptability of RSV vaccination among pregnant women and healthcare professionals.

Germany

On 27 June 2024, the German Standing Committee on Vaccination (STIKO) published a recommendation for universal immunisation of all infants, regardless of risk factors, with a single dose of nirsevimab before or during their first RSV season. Specifically, they recommend that infants born between April and September receive nirsevimab in the autumn before the start of their first RSV season while those born during the usual RSV season (that is, between October and March) receive nirsevimab as soon as possible after birth. Nirsevimab is not recommended for healthy infants whose mothers received RSV vaccination during pregnancy. However, nirsevimab is recommended if maternal vaccination took place less than two weeks before birth. In the case of limited supply, STIKO recommended that nirsevimab be prioritised for infants at high risk of severe RSV-related disease (see risk groups for palivizumab, outlined in Appendix 3A Table 1), as well as infants aged less than six months. STIKO also noted maternal vaccination as a potential alternative strategy to immunisation with nirsevimab. However, having considered the available clinical efficacy and safety data from the NCT04032093 and MATISSE trials, STIKO concluded that there are insufficient data available to inform a recommendation at this time. STIKO noted that it will evaluate its recommendation

and adapt it, if necessary, in line with disease surveillance data, data from post-marketing studies, and new data on maternal vaccination as an alternative immunisation strategy.[72]

The STIKO recommendation in relation to nirsevimab was informed by national and international epidemiology and burden of disease, clinical efficacy and safety trials (D5290C00003, HARMONIE, MEDLEY, and MELODY), preliminary surveillance data for the 2023-2024 RSV season from countries with nirsevimab immunisation programmes (Spain, Luxembourg, and the US), epidemiological modelling and economic evaluation of potential immunisation strategies, potential acceptance of nirsevimab among parents and guardians, and ethical considerations.[72]

In January 2024, prior to the STIKO recommendation, the Federal Joint Committee (G-BA) included nirsevimab in the Medicines Directive and recommended it for children at high risk of severe infection aged less than or equal to one year at the start of the RSV season. Specifically, it is recommended for children:[73, 74]

- who require concomitant therapeutic treatment for BPD
- with hemodynamically relevant congenital heart defects
- with trisomy 21
- aged less than or equal to six months at the start of the RSV season who were born at less than 35 wGA.

The wording of the nirsevimab recommendation was to be updated if the EMA approved a Type II variation request for extension of the nirsevimab indication, to include "children up to 24 months of age who remain vulnerable to serious RSV disease in their second RSV season", with this approval issued by the EMA in June 2024.[49] The G-BA noted that the cost per dose of nirsevimab was €1,350.03 on the Lauer Taxe database as of 1 September 2023.[73] According to a press release from the G-BA on 2 November 2023, RSV antibody prophylaxis in premature infants and children with a high risk of serious illness will be covered by statutory health insurance.[75]

Ireland

In October 2023, the National Immunisation Advisory Committee (NIAC) published recommendations on immunisation against RSV in infants and adults. NIAC recommended that nirsevimab should replace palivizumab for infants at high risk of disease and children who are currently eligible to receive palivizumab,[11] as described in Chapter 18a of the NIAC Immunisation Guidelines (2019)[76] and summarised in Appendix 3A Table 1. This guidance was adapted from the American Academy of Pediatrics (AAP) guidelines. Palivizumab is currently funded by the Health Service Executive (HSE) for this cohort (if administered in the primary care

setting, a co-payment for the drug applies for non-medical card holders).[77] NIAC also recommended the passive immunisation of all infants against RSV during their first RSV season.[11] They noted that both nirsevimab and the maternal vaccine have acceptable safety and efficacy profiles, with a further analysis of cost effectiveness and organisational considerations required to determine the most appropriate immunisation strategy for Ireland.

In April 2024, NIAC published more detailed recommendations in relation to the immunisation of infants with nirsevimab for the 2024-2025 RSV season, as outlined in Appendix 3A Table 1.[78] The updated recommendations advise that nirsevimab administration take place prior to the start of the 2024-2025 RSV season, starting in late September 2024 for all recommended groups born outside the RSV season. They also advise that the youngest infants (that is, those born during the RSV season) and high-risk infants in their first RSV season should be prioritised for nirsevimab in the event of short supply or programmatic limitations.[78] NIAC recommends that the nirsevimab immunisation programme should finish at the end of February 2025, with consideration given to adjusting the start and end dates based on whether or not a catch-up programme is planned and based on levels of circulating RSV, respectively.[78] These updated recommendations did not include any updates in relation to the maternal vaccine.

Both NIAC recommendations were primarily informed by data on the epidemiology and burden of RSV in Ireland and a review of the clinical efficacy and safety data from the pivotal clinical trials involving nirsevimab (D5290C00003, MEDLEY, MELODY, and HARMONIE) and the maternal vaccine (MATISSE); see section 3.4. The updated recommendations were also informed by preliminary surveillance data for the 2023-2024 RSV season in countries that implemented a programme of immunisation with nirsevimab — namely Spain, Luxembourg and the US.

In both sets of recommendations, NIAC noted that acceptability and uptake are critical to consider when determining the best approach to immunisation of infants against RSV, whether through maternal vaccination or neonatal monoclonal antibody prophylaxis. NIAC noted that factors that have previously contributed to successful immunisation uptake should be reflected upon.

As of 1 July 2024, the maternal vaccine is not implemented as part of an immunisation programme in Ireland. As a temporary measure for the 2024-2025 RSV season, the HSE will implement the Pathfinder Programme, which will offer immunisation with nirsevimab to infants born between September 2024 and February 2025.[12] This approach to the immunisation of infants may be modified for the 2025-2026 RSV season based on learnings from the Pathfinder Programme and the findings of this rapid HTA.[12] This approach to the immunisation of infants may

be modified for the 2025-2026 RSV season based on learnings from the Pathfinder Programme, emerging evidence and the findings of this rapid HTA.

Luxembourg

In July 2023, the Higher Council for Infectious Diseases (CSMI) in Luxembourg published recommendations concerning immunisation of infants and children against RSV using nirsevimab for the 2023-2024 RSV season (summarised in Appendix 3A Table 1).[79] Following this recommendation, a national immunisation programme commenced in October 2023 to provide nirsevimab to infants and children for the 2023-2024 RSV season.[80, 81] According to an evaluation of the Luxembourg national RSV immunisation programme, with data from October to mid-December 2023, national coverage with nirsevimab in maternity wards was estimated at 84% (1,277 doses for 1,524 births).[80] There was a 69% decrease in laboratory-confirmed RSV-associated hospitalisations among infants aged less than six months in 2023 compared with 2022 (72 and 232 hospitalised cases, respectively). Among children aged less than five years, there was a 38% decrease in laboratory-confirmed RSV-associated hospitalisations in 2023 compared with 2022 (241 and 389 hospitalised cases, respectively).[80]

In April 2024, the CSMI published updated recommendations.[82] For the 2024-2025 RSV season, immunisation of infants with either nirsevimab or the maternal vaccine is recommended, according to the preferences of parents and healthcare providers. For nirsevimab, one dose is recommended for:

- all infants born from September 2024 to February 2025, preferably to be administered before leaving the maternity ward
- all infants aged less than six months (that is, born between March 2024 and August 2024), to be administered as part of a seasonal campaign starting from September 2024.

For the maternal vaccine, one dose is recommended for healthy women with a healthy single pregnancy and an expected delivery date between September 2024 and February 2025. The maternal vaccine is recommended to be administered between 32 and 36 wGA, and may be co-administered with the influenza vaccine. A two-week interval is recommended between administration of the maternal vaccine and the COVID-19 or Tdap (tetanus, diphtheria and pertussis) vaccines.

The CSMI's recommendations were informed by national and international epidemiology and burden of disease data, the clinical efficacy and safety profile of nirsevimab based on the results of pivotal clinical trials (MELODY, D5290C00003, MEDLEY, and HARMONIE), the effectiveness and safety profile of the maternal vaccine based on results of the MATISSE trial (see section 3.3.3), and preliminary

national surveillance data from the 2023-2024 RSV season including the nirsevimab immunisation programme,[80] as outlined above.

As of 1 July 2024, neither the maternal vaccine nor nirsevimab are eligible for funding.[83, 84]

Netherlands

In February 2024, the Dutch Health Council's Standing Committee on Vaccinations published a report on their advice to the State Secretary of Health, Welfare and Sport regarding immunisation for infants against RSV with nirsevimab or with the maternal vaccine.[85] The Health Council's advice favoured the use of nirsevimab over the maternal vaccine. As summarised in Appendix 3A Table 1, the Health Council advised that nirsevimab be made available as soon as possible and free of charge through the National Immunisation Programme for the following groups:

- for all children born just before or during the RSV season, nirsevimab should be offered as soon as possible after birth (within two weeks at most)
- for all children born after the RSV season, nirsevimab should be offered before the start of their first RSV season.

The Health Council's advice did not include children in their second year of life who are at risk of severe RSV disease, a group who are currently eligible for funding of palivizumab. The Health Council referred the decision on funding of nirsevimab for this group to the Dutch Healthcare Institute.

The Health Council's advice was informed by national and international epidemiology and burden of disease, clinical trials reporting on the efficacy and safety of nirsevimab (D5290C00003, HARMONIE, MELODY, MEDLEY) and the maternal vaccine (MATISSE), preliminary findings from post-implementation surveillance of nirsevimab in Spain,[86] considerations of international practice and acceptability of the interventions, and cost-effectiveness modelling. Details of much of the evidence underpinning the Health Council's advice were published in a 2023 overview report from the Dutch National Institute for Public Health and the Environment (RIVM).[87]

The Health Council acknowledged that there may be challenges associated with implementing their advice. For example, new organisational structures and processes would be required to offer immunisation with nirsevimab within two weeks of birth since, according to the schedule of the National Immunisation Programme at that time, children did not receive their first injection until aged two to three months. Furthermore, the report acknowledged that acceptance was unknown. This included acceptance of nirsevimab specifically, general acceptance of immunisation of infants at a very young age, and, for children born outside of the RSV season, acceptance of

adding an additional injection to those already delivered as part of the National Immunisation Programme.

Norway

The Norwegian Institute of Public Health recommends the maternal vaccine for pregnant women between 24 and 36 wGA and notes that the effect appears best between 30 and 36 wGA.[88] There is no funding for the maternal vaccine (Table 3.2). As of 1 July 2024, nirsevimab is not marketed in Norway.

Spain

In July 2023, the Spanish Ministry of Health published the recommendations of the Public Health Commission on the use of nirsevimab for the 2023-2024 RSV season,[89] as summarised in Appendix 3A Table 1. According to these temporary recommendations, nirsevimab was recommended, in order of priority, for infants at high risk of severe RSV disease and infants aged less than six months at the beginning of, or during, the RSV season (October to March). The recommendations were informed by an assessment that considered national and international data on the epidemiology and burden of disease associated with RSV infection, and the clinical efficacy and safety results of pivotal clinical trials involving nirsevimab (D5290C00003, MELODY, MEDLEY, and HARMONIE). See section 3.4.

In March 2024, updated temporary recommendations for the use of nirsevimab for the 2024-2025 RSV season were published by the Ministry of Health.[90] The immunisation campaign is due to start in October 2024, but may be brought forward if deemed appropriate. It will offer immunisation to all infants born from 1 April 2024 to 31 March 2025 either as part of a catch-up programme for those born outside the RSV season or as soon as possible after birth (preferably in the first 24 to 48 hours) for those born during the RSV season.[90] As in the 2023-2024 season, nirsevimab will be prioritised for infants at high risk of severe RSV disease, infants born during the RSV season, and infants who are aged less than six months at the start of the RSV season. These updated recommendations were based on preliminary data for the 2023-2024 RSV season in Spain, since the recommendations were published prior to the end of that season. This included data on nirsevimab administration, weekly RSV incidence rates and hospitalisations, and limited data on effectiveness, safety and acceptability.

The respective autonomous communities of Spain were responsible for deciding on their approach to and timing of implementation of the recommendations on the use of nirsevimab for the 2023-2024 RSV season, and also for agreeing contracts for the supply of nirsevimab. In March 2023, Galicia introduced free universal RSV prophylaxis for infants using nirsevimab into its immunisation schedule on a pilot

basis for the 2023-2024 RSV season.[86] The contracted cost per dose for the 2023-2024 season was €209 for both the 50mg and 100mg syringes.[91] The immunisation programme in Galicia was structured around three immunisation groups:[92]

- seasonal immunisation within the first 24 hours after birth for infants born between 25 September 2023 and 31 March 2024
- catch-up immunisation at the beginning of the RSV season for infants born between 1 April 2023 and 24 September 2023
- immunisation of infants at high risk of disease aged less than 24 months, born between 1 October 2021 and 31 March 2023.

The NIRSE-GAL study, which is evaluating the impact of the immunisation programme against RSV in Galicia, reported on data up to 25 February 2024 (from week 40 until week 8).[93] Immunisation coverage was 92.7% at birth, 79.6% for the catch-up, and 100% for the high-risk groups. The number of RSV-associated hospitalisations for the 2023-2024 season was compared with the median number of hospitalisations for the 2017-2018 to 2019-2020 RSV seasons. When compared with previous seasons, there was an 88.5% decrease in RSV-associated hospitalisations among infants aged less than six months.[93]

In February 2024, initial results were published for hospital-based surveillance of the nirsevimab immunisation campaign from nine hospitals of three other autonomous regions of Spain.[94] The surveillance period was from 1 October 2023 to between 5 and 15 January 2024. In total, 15,676 infants were eligible for immunisation across the three regions. Immunisation coverage varied by region, with an average coverage rate of 89.8% in Valencia, 88.9% in Murcia and 98.6% in Valladolid. There were 166 hospital admissions for LRTI during the period, of which 95 were positive for RSV. Among these 95 RSV hospital admissions, 59% (n=56/95) had been immunised. The estimated effectiveness of immunisation with nirsevimab against RSV-associated LRTI hospitalisations was reported as 69.3% (95% CI: 36.4 to 86.2), 86.9% (95% CI: 77.1 to 92.09) and 97.0% (95% CI: 87.7 to 99.6), respectively, in the three autonomous regions. The pooled effectiveness estimate against RSV-associated LRTI hospitalisations was 84.4% (95% CI: 76.8 to 90.0).

According to the BIFIMED search engine, which provides information relating to the financing of authorised medicines in Spain, nirsevimab and the maternal vaccine are fully funded as of 1 July 2024.[95, 96] As of 1 July 2024, the cost per dose of nirsevimab for the 2024-2025 season in each autonomous community season is uncertain.

Sweden

As a precursor to a full update of their recommendation, the Swedish Medical Products Agency published a temporary recommendation regarding prophylaxis against severe RSV infection in children in September 2023 to inform the 2023-2024 RSV season.[97] The temporary recommendations for antibody prophylaxis with palivizumab and nirsevimab are listed in order of priority, with those at high risk of severe RSV-associated disease given higher priority. Full details are summarised in Appendix 3A Table 1.

The Swedish Medical Products Agency published the full update to their recommendation in May 2024,[98] together with a summary report on the evidence used to support the recommendation.[99] The recommendation states that prophylaxis with monoclonal antibodies reduces the risk of severe RSV disease and the need for hospitalisation in infants aged 0 to 12 months, with nirsevimab recommended over palivizumab. The recommendation notes that, while all infants can benefit from nirsevimab, infants at high risk should be prioritised if availability is limited. The order of priority is as per the risk groups listed in the temporary recommendation for the 2023-2024 season (see Appendix 3A Table 1). Nirsevimab is also recommended for all infants in their first RSV season if the mother is not vaccinated, or is vaccinated less than 14 days before birth. If the mother is vaccinated more than 14 days before birth, nirsevimab is recommended for infants born at less than 32 wGA and for infants at high risk of severe RSV disease born at or greater than 32 wGA. Nirsevimab is not recommended for infants without risk factors born at or greater than 32 wGA, if the mother was vaccinated more than 14 days before birth.[98]

In the May 2024 recommendation, nirsevimab is recommended for children aged up to 24 months who are at high risk of severe RSV disease during their second RSV season. If nirsevimab is not available, palivizumab is recommended for this group.[98] As of 1 July 2024, nirsevimab was not available in Sweden.

Details regarding the implementation of these recommendations were not identified. No information in relation to funding of nirsevimab or the maternal vaccine was identified.[100] The Public Health Agency of Sweden has planned an assessment of the maternal vaccine against RSV.[101]

UK

In September 2023, the Joint Committee on Vaccination and Immunisation (JCVI) advised that a cost-effective RSV immunisation programme should be developed for infants and older adults.[102] This advice was informed by an evaluation of the national epidemiology and burden of disease associated with RSV infection, clinical efficacy and safety data from the pivotal clinical trials for nirsevimab (MELODY and

HARMONIE) and the maternal vaccine (MATISSE), and modelling of the impact and cost effectiveness of potential immunisation strategies.[102]

The JCVI advised a preference for a year-round immunisation programme to ensure high uptake and operational effectiveness, as it would be less complex and resource intensive to deliver compared with seasonal campaigns. The JCVI advised that it did not have a preference for either nirsevimab or the maternal vaccine, and both options should be considered for a universal programme. This advice was in addition to advice from the JCVI in February 2023, that palivizumab should be replaced by nirsevimab for those currently eligible to receive palivizumab, due to its extended half-life, high efficacy, and single dose requirement.[102]

In June 2024, the UK Health Security Agency published correspondence detailing the introduction of two new nationally-funded NHS vaccination programmes against RSV: one for the immunisation of infants through maternal vaccination during pregnancy, and one for the vaccination of older adults.[103] From 1 September 2024, women who are at least 28 weeks pregnant should be offered a single dose of the RSV vaccine (RSVpreF – Abrysvo®), ideally at the 28-week antenatal visit. Pregnant women will remain eligible to be vaccinated up to birth, with vaccination offered on a year-round basis. As highlighted in section 3.1.1, infants at increased risk of RSV disease will continue to be offered passive immunisation with palivizumab, regardless of whether the mother was vaccinated during pregnancy.

Table 3.2 Summary of practices with respect to immunisation against RSV in infants and young children in EU/EEA countries and the UK, as of 1 July 2024

Country	Practice	Palivizumab	Nirsevimab	Maternal vaccine
Austria	Recommended:	✓	✓	✓
	Available:	✓	X	✓
	Funded:	X	N/A	X
	Immunisation programme:	N/A	X	X
Belgium	Recommended:	✓	✓	✓
	Available:	✓	X	✓
	Funded:	✓	✓	X
	Immunisation programme:	N/A	X	N/I
Bulgaria	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Croatia	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Cyprus	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	N/I	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Czech Republic	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	✓
	Funded:	✓	X	✓§
	Immunisation programme:	N/A	N/A	N/I
Denmark	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	✓

Country	Practice	Palivizumab	Nirsevimab	Maternal vaccine
	Funded:	N/I	N/A	X
	Immunisation programme:	N/A	N/A	X
Estonia	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	X	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Finland	Recommended:	✓	N/I	X
	Available:	✓	X	✓
	Funded:	X	N/A	X
	Immunisation programme:	N/A	N/A	N/I
France	Recommended:	✓	✓	✓
	Available:	✓	✓	N/I
	Funded:	X	✓‡	N/I
	Immunisation programme:	N/A	✓	✓
Germany	Recommended:	✓	✓	X*
	Available:	✓	✓	✓
	Funded:	✓	✓	N/A
	Immunisation programme:	N/A	X	N/A
Greece	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	N/I	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Hungary	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Iceland	Recommended:	X	N/I	N/I
	Available:	✓	X	✓

Country	Practice	Palivizumab	Nirsevimab	Maternal vaccine
	Funded:	X	N/I	X
	Immunisation programme:	N/A	X	X
Ireland	Recommended:	✓*	✓*	✓*
	Available:	✓	N/I+	✓
	Funded:	✓	✓*+	X
	Immunisation programme:	N/A	✓*+	X*
Italy	Recommended:	✓	N/I	N/I
	Available:	✓	✓	✓
	Funded:	✓	X	X*
	Immunisation programme:	N/A	N/A	N/A
Latvia	Recommended:	✓	N/I	N/I
	Available:	✓	X	X
	Funded:	X	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Liechtenstein	Recommended:	✓	N/I	N/I
	Available:	✓	X	X
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Lithuania	Recommended:	✓	N/I	N/I
	Available:	✓	X	X
	Funded:	X	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Luxembourg	Recommended:	✓	✓	✓
	Available:	✓	✓	✓
	Funded:	✓	X	X
	Immunisation programme:	N/A	N/I†	N/I
Malta	Recommended:	✓	N/A	N/I
	Available:	X	X	X

Country	Practice	Palivizumab	Nirsevimab	Maternal vaccine
	Funded:	N/A	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Netherlands	Recommended:	✓	✓	✓
	Available:	✓	N/I	✓
	Funded:	✓	X*	X
	Immunisation programme:	N/A	X*	X
Norway	Recommended:	✓	X¥	✓
	Available:	✓	X	✓
	Funded:	✓	N/A	X
	Immunisation programme:	N/A	N/A	X
Poland	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Portugal	Recommended:	✓	N/I	N/I
	Available:	✓	✓	✓
	Funded:	X	X	X
	Immunisation programme:	N/A	N/A	N/A
Romania	Recommended:	N/I	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Slovakia	Recommended:	✓	N/I	N/I
	Available:	✓	N/I	N/I
	Funded:	✓≠	N/A	N/A
	Immunisation programme:	N/A	N/A	N/A
Slovenia	Recommended:	✓	N/I	X*
	Available:	✓	N/I	N/I

Country	Practice	Palivizumab	Nirsevimab	Maternal vaccine
	Funded:	✓	N/A	N/A
	Immunisation programme:	N/A	N/A	X*
Spain	Recommended:	✓	✓*	X*
	Available:	✓	✓	✓
	Funded:	✓	✓	✓
	Immunisation programme:	N/A	✓	X
Sweden	Recommended:	✓	✓	X*
	Available:	✓	X	✓
	Funded:	✓	N/A	N/I
	Immunisation programme:	N/A	N/A	N/I
United Kingdom	Recommended:	✓	✓	✓
	Available:	✓	X	✓
	Funded:	✓	X	✓
	Immunisation programme:	N/A	X	✓

Key: N/A – not applicable; N/I – no information identified.
Note: Information on palivizumab is provided in relation to recommendations, availability and funding; information on its inclusion in an immunisation programme is considered 'not applicable', since it is only authorised for use in infants at high risk of severe RSV disease and not as a universal immunisation programme for the general infant population.
* Ongoing assessment, as of 1 July 2024.
§ Eligible for partial funding through health insurance.
‡ Partial reimbursement at 30% for the 2024-2025 RSV season.
+ Will be available and funded as part of a temporary immunisation programme from September 2024 to February 2024.
† Nationwide immunisation campaigns undertaken for the 2023-2024 RSV season.
¥ If it becomes available, the Norwegian Association of Paediatricians will recommend that nirsevimab be chosen over palivizumab for practical reasons, subject to price.
≠Subject to prior approval of health insurance company.

USA

In Ireland, the 2023 NIAC guidance on palivizumab prophylaxis for infants and young children was adapted from the American Academy of Pediatrics (AAP).[76] In July 2023, the Food and Drug Administration (FDA) approved nirsevimab for the prevention of RSV-associated LRTI among infants and children aged less than 24 months. In February 2024, the AAP published updated recommendations for the use of nirsevimab to prevent RSV disease in infants and young children.[104] The AAP state that their recommendations are consistent with those of the Advisory Committee on Immunization Practices (ACIP), published in August 2023,[105] that recommend nirsevimab for:

- Infants aged less than eight months born during or entering their first RSV season and whose pregnant parent did not receive the maternal vaccine or their vaccination status is unknown, or who were born less than 14 days after the maternal vaccine was administered.
    - Nirsevimab may be considered for infants aged less than eight months and born to a vaccinated pregnant parent in rare circumstances, when clinical judgement decides administration is warranted, such as:
        - pregnant people with immunocompromising conditions that may prevent them from mounting an adequate immune response to vaccination or who have conditions associated with reduced transplacental antibody transfer (for example, human immunodeficiency virus (HIV) infection)
        - infants who might have experienced loss of transplacentally acquired antibodies (for example, due to extracorporeal membrane oxygenation)
        - infants with substantially increased risk for severe RSV disease (for example, due to HS-CHD).
- Infants and children aged between 8 and 19 months of age who are at increased risk of severe RSV disease and entering their second RSV season, including those recommended by the AAP to receive palivizumab,[38] regardless of RSV vaccination status of the pregnant parent, such as:
    - infants and children with chronic lung disease (CLD) of prematurity who required medical support at any time up to six months before the start of the second RSV season

- infants and children who are severely immunocompromised
- infants and children with cystic fibrosis who have manifestations of severe lung diseases or have weight-for-length that is less than the 10th percentile.

In addition, the AAP[104] and ACIP[105] noted several considerations regarding the administration of nirsevimab:

- clinicians should aim to administer nirsevimab in the first week of life, in hospital or in the outpatient setting, for infants born close to or during the RSV season
- infants with prolonged hospitalisation should receive nirsevimab shortly before or soon after discharge from hospital
- nirsevimab should be administered to other eligible infants and young children shortly before or during the RSV season, as soon as nirsevimab is available
- nirsevimab may be administered from October through the end of March in most of the continental US; however, providers may adjust the timing of administration of nirsevimab based on guidance from public health authorities or regional medical centres
- administration of nirsevimab with age-appropriate vaccines is recommended, in accordance with CDC guidance.

These recommendations were informed by work undertaken by the ACIP Maternal and Pediatric RSV Work Group. Since October 2021, this Work Group has reviewed the evidence of the safety and efficacy of nirsevimab among infants and young children (to include GRADE assessments of the certainty of evidence and use of the Evidence to Recommendation framework to guide deliberations on the recommendations for nirsevimab).[106, 107] In addition, the cost effectiveness of nirsevimab for infants aged less than eight months (at $445 per dose) was estimated at $102,811 per quality adjusted life year (QALY) gained. Compared with infants during their first RSV season, the cost effectiveness of nirsevimab for children entering their second RSV season (at $890 per dose, assuming 200mg dose is twice the price of the 100mg dose) was estimated at $1,557,544 per QALY gained.

At their meeting in June 2024, the ACIP concluded that those who received the maternal vaccine during a previous pregnancy are not recommended to receive additional doses during future pregnancies; instead, their infant should receive nirsevimab. This recommendation was based on data from older adult cohorts

whereby revaccination did not restore antibody levels to previous levels. The ACIP note that this recommendation may be updated in the future if additional data are available.[108]

3.3.3 Summary of the clinical trials that informed countries' recommendations for infants

Nirsevimab

D5290C00003 phase 2b trial

The D5290C00003 trial assessed the safety and efficacy of nirsevimab in healthy preterm infants born from 29 to less than 35 wGA and aged one year or younger entering their first RSV season;[109] EU participants had to be aged eight months or younger. The trial was conducted at 164 sites in 23 countries. Participants were excluded if they were eligible to receive palivizumab, had an acute illness at time of randomisation, previously had an RSV infection or had previously been exposed to any other investigational product for RSV prevention. All infants were randomised to receive either one intramuscular injection of 50mg nirsevimab (n=969) or placebo (n=484) from November 2016 through November 2017. The primary end point was medically attended RSV-associated LRTI through 150 days after administration. The secondary efficacy end point was hospitalisation for RSV-associated LRTI through 150 days after administration.

The incidence of medically attended RSV-associated LRTI was 70.1% (95% confidence interval (CI), 52.3 to 81.2) lower in the nirsevimab group compared with placebo (2.6% (n=25 infants) versus 9.5% (n=46 infants); p<0.001). The incidence of hospitalisation for RSV-associated LRTI was 78.4% (95% CI, 51.9 to 90.3) lower in the nirsevimab group compared with placebo (0.8% (n=8 infants) versus 4.1% (n=20 infants); p<0.001). In the placebo group, five participants were admitted to the intensive care unit (ICU) and four received assisted ventilation due to RSV infection; there were no ICU admissions in the nirsevimab group. Among participants with medically attended RSV-associated LRTI, 16% (n=4) of the nirsevimab group and 32.6% (n=15) of the placebo group received supplemental oxygen.

The types and frequencies of adverse events were reported as similar between the nirsevimab and placebo groups. Serious adverse events were reported in 11.2% (n=108) of the nirsevimab group and 16.9% (n=81) of the placebo group, although the investigator considered none to be related to the intervention. The majority of adverse events were of grade one or grade two severity. Adverse events of special interest were reported in 0.5% (n=5) of the nirsevimab group and 0.6% (n=3) of the placebo group, namely: rash (nirsevimab, n=4; placebo, n=3) and petechiae (nirsevimab, n=1). These adverse events of special interest were considered to be

related to nirsevimab. Six deaths occurred (nirsevimab, n=2; placebo, n=4), but none were known to be due to RSV or considered related to the interventions by the investigator.

MELODY phase 3 trial

The MELODY trial assessed the efficacy and safety of nirsevimab in healthy, late preterm infants (born at 35 wGA or more) and term infants.[110] Eligible infants had to be aged one year or less and entering their first RSV season. Infants were excluded if they met eligibility criteria to receive palivizumab, had any fever or acute illness within seven days before randomisation, or had RSV infection before or at randomisation. Participants were randomised to receive either nirsevimab (n=994) at a dose of 50mg if they weighed less than 5kg or 100 mg if they weighed 5kg or more, or placebo (n=496). The primary end point was medically attended RSV-associated LRTI through 150 days after injection. The secondary efficacy end point was hospitalisation for RSV-associated LRTI through 150 days after injection.

The majority of the infants in the trial were born at term (86.0%, n=1,281). The incidence of medically attended RSV-associated LRTI was 74.5% (95% CI, 49.6 to 87.1) lower in the nirsevimab group compared with placebo (1.2% (n=12 infants) versus 5.0% (n=25 infants); p<0.001). The incidence of hospitalisation for RSV-associated LRTI was 62.1% (95% CI, -8.6 to 86.8) lower in the nirsevimab group compared with placebo (0.6% (n=6 infants) versus 1.6% (n=8 infants); p<0.07); this was not statistically significant.

The types and frequencies of adverse events that occurred throughout the trial were reported as similar between the two groups. The majority of adverse events were grade one or grade two. Adverse events of grade three severity or higher were reported in 3.6% of the nirsevimab group (n=36) and 4.3% of the placebo group (n=21). There were serious adverse events reported in 6.8% of the nirsevimab group (n=67) and 7.3% of the placebo group (n=36). Three deaths occurred in the nirsevimab group: one death (at day 140) was of unknown cause in an infant with failure to thrive; two deaths (at day 143 and day 338) were attributed to gastroenteritis. None of the serious adverse events or deaths were considered by the investigator to be related to nirsevimab or the placebo. One adverse event of special interest was reported in the nirsevimab group: a grade three generalised macular rash appeared six days after injection, which did not require treatment and resolved after 20 days. The investigator considered this event to be related to nirsevimab.

MEDLEY phase 2/3 trial

The MEDLEY trial assessed the safety of nirsevimab compared with palivizumab in infants born at or before 35 wGA who did not have early onset congenital heart

disease (CHD) or chronic lung disease (CLD) (preterm cohort), and in infants who had uncorrected, partially corrected, or medically treated CHD or CLD requiring therapeutic intervention within six months (CHD-CLD cohort).[111] The preterm cohort (n=615) and the CHD-CLD cohort (n=310) were randomised to receive either palivizumab (preterm cohort n=206, CHD-CLD cohort n=98) or nirsevimab (preterm cohort n=406, CHD-CLD cohort n=208).

The safety profile and incidence of adverse events was reported as similar across the treatment groups and cohorts. Two adverse events of special interest were reported in the nirsevimab group: heparin-induced thrombocytopenia in infants with CHD and maculopapular rash following a placebo dose in a preterm infant. Five deaths occurred in the nirsevimab group: two in the preterm cohort and three in the CHD-CLD cohort. One death occurred in the palivizumab group of the CHD-CLD cohort. All deaths were considered unrelated to treatment by the investigator.

HARMONIE phase 3 trial

The HARMONIE trial assessed the efficacy and safety of nirsevimab in infants born at 29 wGA or more, aged one year or less and entering their first RSV season.[112] Infants were excluded if they met eligibility criteria to receive palivizumab, had any fever or acute illness within seven days before randomisation, or had RSV infection before or at randomisation. Infants were randomised to receive either nirsevimab (n=4,037) or standard care (n=4,021) (that is, no intervention) before or during the RSV season. The primary end point was hospitalisation for RSV-associated LRTI, defined as hospital admission and a positive RSV test result. The secondary end point was very severe RSV-associated LRTI, defined as hospitalisation for RSV-associated LRTI with an oxygen saturation of less than 90% and requiring supplemental oxygen.

The incidence of hospitalisation for RSV-associated LRTI was 83.2% (95% CI, 67.8 to 92.0) lower in the nirsevimab group compared with the standard care group (0.3% (n=11 infants) versus 1.5% (n=60 infants); p<0.001). The efficacy of nirsevimab in preventing hospitalisation for RSV-associated LRTI was demonstrated independently in the three trial sites: France (89.6% (adjusted 95% CI, 58.8 to 98.7); multiplicity adjusted p<0.001); Germany (74.2% (adjusted 95% CI, 27.9 to 92.5); multiplicity adjusted p=0.006); and the UK (83.4% (adjusted 95% CI, 34.3 to 97.6); multiplicity adjusted p=0.003). The incidence of very severe RSV-associated LRTI was 75.7% (95% CI, 32.8 to 92.9) lower in the nirsevimab group compared with the standard care group (0.1% (n=5 infants) versus 0.5% (n=19 infants); p<0.004).

The majority of adverse events in the two trial groups were grade one or grade two severity. One infant had a grade three serious adverse event (infantile spasms) 23

days after receiving nirsevimab that was considered to be related to the intervention. The authors noted that the occurrence of this event was within the background rate for a trial of this size. Two infants discontinued the trial due to safety events: one infant in the nirsevimab group had a serious adverse event (facial bruising) that was considered not related to the trial treatment; one infant in the standard care group had grade two bronchiolitis and received palivizumab treatment. No deaths were reported in either group.

MUSIC phase 2 trial

The MUSIC open label trial assessed the safety and tolerability of nirsevimab for the prevention of RSV disease in children with immunocompromising conditions aged 24 months or less.[113] Children with one or more immunocompromising conditions received a single intramuscular injection of nirsevimab 50mg (for those weighing less than 5kg) or 100mg (for those weighting 5kg or more) prior to their first RSV season. Those entering their second RSV season received 200mg of nirsevimab. Adverse events of special interest included immediate hypersensitivity, immune complex disease, or thrombocytopenia.

There were 100 children enrolled in the trial from eight countries; 46 children were entering their first RSV season and 54 were entering their second. Immunocompromising conditions included primary immunodeficiency (n=33), systemic high-dose corticosteroid therapy (n=29), immunosuppressive chemotherapy (n=20), history of organ or bone marrow transplant (n=16), other immunosuppressive therapy (n=15), and HIV infection (n=8); children may have had more than one condition. Eight treatment-related adverse events were reported in six children (pyrexia n=4, abdominal pain n=1, erythema n=1, rash n=2). No treatment-related serious adverse events were reported. Three deaths were reported (LRTI, septic shock, and suspected tumour haemorrhage) and all were determined to be unrelated to treatment.

Treatment-emergent anti-drug antibodies (ADA) developed in 11 children (two by day 151, nine by day 361), of whom one experienced a grade one treatment-related adverse event (pyrexia within 60 minutes of dosing). ADA-positive children were more likely to have nirsevimab levels below the limit of detection, compared with ADA-negative children. The authors reported that nirsevimab serum levels at day 151 were similar to levels demonstrated in the MELODY trial, but fourteen children demonstrated a rapid decline in serum concentrations through day 151, of whom nine had protein-losing conditions.

Summary of evidence appraisals of nirsevimab conducted by identified countries

The following observations were noted by countries that included an evidence summary or evaluation of clinical trial results pertaining to nirsevimab:

- As part of a rapid review, the Belgian Health Care Knowledge Centre (KCE) pooled the results of the D5290C00003 and MELODY trials in a meta-analysis; the vaccine efficacy against medically attended RSV-associated LRTI was 75% (95% CI: 66 to 82) and vaccine efficacy against RSV-related hospitalisations was 79% (95% CI: 63 to 88).[114]
    - Following the GRADE methodology, the overall quality of evidence was judged as high quality by the KCE.
    - Quality appraisal by the KCE included the D5290C00003 and MELODY trials, with both studies judged as being at low risk of bias. The report authors noted potential grounds for downgrading the overall quality of evidence score to moderate quality for indirectness of results due to the exclusion of infants with any history of LRTI. The results were noted as consistent with the preliminary findings from the HARMONIE trial.
- In presentations to the ACIP in February 2023, the National Center for Immunization and Respiratory Diseases (NCIRD) judged the overall quality of evidence, as per GRADE methodology, as moderate quality for nirsevimab administered in the first year of life (that is, aged less than eight months entering their first RSV season) and as very low quality for nirsevimab administered to children at increased risk of severe disease and in the second year of life (that is, aged less than 20 months entering their second RSV season).[115-117]
    - Quality appraisal by the NCIRD included the D5290C00003 and MELODY trials.
    - The NCIRD considered that, in the first year of life, nirsevimab was effective at preventing medically attended RSV-associated LRTI (high certainty of evidence), RSV-associated LRTI with hospitalisation (high certainty of evidence), all-cause medically attended LRTI (high certainty of evidence) and all-cause LRTI-associated hospitalisation (high certainty of evidence).
    - The NCIRD considered that nirsevimab was likely effective at preventing medically attended RSV-associated LRTI with ICU admission in the first year of life (moderate certainty of evidence). This outcome was downgraded for serious concern about imprecision due to the small number of events noted in the trial.

- The NCIRD considered that serious adverse events were likely not more common in the nirsevimab group compared with the placebo group in the first year of life (moderate certainty of evidence). This outcome was downgraded for serious concern about imprecision, as efficacy trials are not powered to detect rare events.
- The NCIRD considered that, in the second year of life, pre-determined thresholds were met for the extrapolation of efficacy of nirsevimab at preventing medically attended RSV-associated LRTI in infants aged less than 12 months to pharmacokinetic levels in children aged less than two years with CLD or CHD entering their second RSV season (low certainty of evidence). This outcome was downgraded twice for serious concern about indirectness due to the use of surrogate outcomes and the mismatch between the trial population and proposed indication.
- The NCIRD considered that, in the second year of life, serious adverse events may not be more common in the nirsevimab group compared with the placebo group (very low certainty of evidence). This was downgraded for indirectness as the comparison group is palivizumab rather than placebo, and for serious concern about imprecision due to the width of the confidence intervals.

- In Germany, the STIKO assessed the overall quality of the evidence in relation to the efficacy and safety of nirsevimab using the GRADE methodology.[72, 118] This was based on a January 2024 update of the systematic review originally conducted by the NCIRD to inform the ACIP recommendations.
  - Similar to the KCE, STIKO pooled the results of the D5290C00003 and MELODY trials in a meta-analysis. The STIKO reported the efficacy in preventing hospitalisation due to RSV-associated LRTI was 80% (95% CI: 68 to 88), and the efficacy in preventing severe RSV-associated LRTI requiring intensive care was 81% (95% CI: 62 to 90).
  - STIKO considered the certainty of the evidence to be high for all efficacy outcomes.
  - STIKO pooled safety results from the D5290C00003, MELODY and HARMONIE trials. They reported that the relative risks of adverse events and serious adverse events were similar in those who received nirsevimab compared with placebo, with high and moderate certainty of evidence, respectively.
  - Adverse events of special interest (for example, anaphylaxis, immune complex disorders, and thrombocytopenia) were included as an

additional safety outcome by STIKO, and were found to be rare overall (n=16/12,476). However, STIKO noted that the pooled study population was too small to detect rare events such as anaphylaxis, which was not reported in any study.

- In France, the Transparency Commission of the HAS noted several limitations in the available clinical trial data:[119]
    - The Commission noted that there is a lack of evidence directly demonstrating superiority or non-inferiority of nirsevimab compared with palivizumab; the clinical data supporting the use of nirsevimab in patients eligible to receive palivizumab is from the MEDLEY trial, in which the effectiveness of nirsevimab in infants at high risk of serious RSV disease is extrapolated from the D5290C0003 and MELODY trial results based on pharmacokinetic exposure.
    - The Commission also noted that there is an absence of data on the potential impact of nirsevimab in reducing the length of hospitalisation and ICU admission.
- Reports from Belgium, France and Germany noted an absence of data on the potential impact of nirsevimab on mortality.[114, 119, 120]
- A report by the Higher Council for Infectious Diseases (CSMI) in Luxembourg noted:[79]
    - There are limited data available in extremely preterm infants (that is, infants born at less than 29 wGA) aged less than eight weeks.
    - Based on two decades of data using palivizumab without interference with the immune response to vaccinations in infants and young children, the CSMI considered that immunisation with nirsevimab is not expected to interfere with vaccinations and can be co-administered at different anatomical sites.
- A report by the Standing Committee on Vaccinations of The Health Council of the Netherlands noted that there was no evidence to indicate that immunisation with nirsevimab in the first year of life leads to a shift in the burden of disease to the second year of life.[121]
- Reports from France, the Netherlands and Spain noted that the potential risk for the emergence of RSV strains resistant to nirsevimab cannot be ruled out based on the available clinical data, although there does not appear to be evidence for this currently.[119, 121, 122]

Maternal vaccine

Phase 2b trial (NCT04032093)

A report on a planned interim analysis of the NCT04032093 phase 2b trial described the efficacy, immunogenicity, and safety of the RSVpreF vaccine in pregnant women and their infants.[123] In this trial, 403 pregnant women (at 24 to 36 wGA) were randomised to receive either 120µg or 240µg of RSVpreF vaccine (with or without aluminium hydroxide adjuvant) or placebo. The 120µg RSV vaccine antigen without adjuvant is the dose and formulation that has since received marketing authorisation from the EMA.

In terms of immunogenicity, 50% titres of RSV A, B, and combined A/B neutralising antibodies were higher in both maternal and infant samples at birth in vaccine recipients compared to placebo recipients. The levels of RSV neutralising titres in umbilical cord blood did not vary substantially according to gestational age at the time of immunisation. With immunisation occurring at 24 to 36 wGA, the authors noted that these findings support an immunisation window over approximately three months of pregnancy.

The most common local reaction was mild-to-moderate injection site pain, reported by 29.5% of participants in the 120µg RSVpreF vaccine group compared with 10.1% of the placebo group. Most systemic reactions were mild or moderate and were similar in the RSVpreF vaccine and placebo groups, with the exception of muscle pain, which was reported more frequently in the RSVpreF vaccine groups (26.9% of the 120µg RSV vaccine group compared with 12.7% of the placebo group). The authors outlined that there were no notable between-group differences in reported unsolicited adverse events within one month after vaccination. The most reported categories of adverse events were infections, gastrointestinal disorders, and pregnancy-related conditions, including preterm delivery; the frequency of these events was similar in all the groups. Serious adverse events were reported by less than 5% of the participants during the month after vaccination. No adverse events were considered by the investigators to be related to vaccination. In total, 55 serious adverse events were reported in 43 maternal participants (10.6% of the total cohort). Of these events, 84% were directly related to complications of pregnancy, labour, delivery, and the immediate post-partum period. None of the serious adverse events were considered by the investigators to be related to vaccination. Similarly, 170 of 403 infants (42.2%) experienced an adverse event in their first month of life, with these events occurring at a similar frequency between trial groups. None of the adverse events were considered by the investigators to be related to maternal vaccination.

Phase 2b trial (NCT04071158)

The NCT04071158 phase 2b, placebo-controlled, observer-blind, non-inferiority study evaluated safety, tolerability and immunogenicity of RSVpreF through a one-month follow-up period when administered concomitantly with the Tdap vaccine in non-pregnant women aged 18 to 49 years.[124] Participants were randomised to one of five vaccine groups, two of which received the same RSVpreF vaccine composition as brought to market (that is, 120µg RSV vaccine antigen without adjuvant). In total, 141 participants received 120µg RSVpreF administered concomitantly with placebo (normal sterile saline), a further 141 participants received 120µg RSVpreF with Tdap, and 141 participants received placebo and Tdap.

RSVpreF was considered to be safe and well tolerated when administered with Tdap or alone. Local reactions and systemic events occurred at similar frequencies across the 120µg RSV vaccine and placebo groups, were mostly mild or moderate in severity, and of short duration (that is, median durations of one to three days). One participant (n=1/141, 0.7%) in the RSVpreF 120µg with Tdap group reported severe pain at the injection site. In total, three participants reported a grade 4 fever (that is, greater than 40.0°C): two in the RSVpreF 120µg with Tdap group (n=2/141, 1.4%) and one in the placebo with Tdap group (n=1/141, 0.7%). The authors noted that no serious, immediate or life-threatening adverse events were reported within one month of vaccination, no adverse events led to withdrawal from the study, and no deaths occurred during the study. Two severe adverse events were considered related to the vaccine: one case of constipation in the RSVpreF 120µg with placebo group (n=1/141, 0.7%) and one case of lymphadenopathy in the RSVpreF 120µg with Tdap group (n=1/141, 0.7%).

RSV-A and RSV-B neutralising responses were non-inferior for RSVpreF administered concomitantly with Tdap compared with RSVpreF alone. Equally, immune responses were non-inferior for the tetanus and diphtheria components of Tdap when administered with RSVpreF. However, reduced pertussis component antibody responses were observed for concomitant administration of Tdap with RSVpreF compared with administration of Tdap alone. The authors noted that the reasons for the observed pertussis responses were not known, and that further studies were required to determine the clinical significance of these findings.

MATISSE phase 3 trial

The Maternal Immunization Study for Safety and Efficacy (MATISSE) trial, sponsored by Pfizer, assessed the efficacy and safety of the RSVpreF vaccine.[125] This maternal vaccine was given as a singular intramuscular injection of 120µg to pregnant women at 24 to 36 wGA. Women with high-risk pregnancies were excluded, such as those with a current risk of preterm birth, multiple pregnancy, or a previous infant with a clinically significant congenital anomaly. The participants were randomised to receive

either the vaccine (n=3,682 mothers) or placebo (n=3,676 mothers), with 3,570 and 3,558 infants, respectively, subsequently evaluated. The two primary efficacy end points were medically attended severe-RSV associated LRTI and medically attended RSV-associated LRTI in infants within 90, 120, 150, and 180 days after birth. The success criterion for vaccine efficacy for the primary end points was considered met if the lower boundary of the CI (99.5% CI at 90 days and 97.58% CI at later intervals) was greater than 20%.

In April 2023, a prespecified interim analysis was published.[126] At that time, 97.2% of the vaccine group and 97.1% of the placebo group had given birth, with 79.4% and 79.6% of those who had given birth, respectively, having completed the trial. Data from 85% of the scheduled follow-up through 180 days were available, with 96%, 79% and 46% of infants completing 1-month, 6-month, and 12-month follow up, respectively. A significant reduction in the incidence of medically attended severe RSV-associated LRTI was noted in the vaccinated group within 90 days after birth (0.2% versus 0.9%; vaccine efficacy (VE) 81.8% [99.5% CI, 40.6 to 96.3]) and within 180 days after birth (0.5% vs. 1.8%; VE: 69.4% [97.58% CI, 44.3 to 84.1]). While fewer cases of medically attended RSV-associated LRTI occurred within 90 days after birth in the vaccinated cohort (0.7% vs. 1.6%), the statistical success criterion was not met (VE 57.1% [99.5% CI, 14.7 to 79.8]).

Local reactions were more frequently reported by maternal participants in the vaccine group than in the placebo group, with injection-site pain the most common local reaction reported (41% in the vaccine group versus 10% in the placebo group). Of note, statistical significance was not reported for any safety outcomes in this study. The percentages of maternal participants who reported systemic events within seven days after injection were similar in the two groups, but two events were reported more frequently in the vaccine group: muscle pain (27% vs. 17%) and headache (31% vs. 28%). The authors reported that serious adverse events among maternal participants through six months after injection were similar between the groups; the most frequent were pre-eclampsia (1.8% in vaccine recipients versus 1.4% in placebo recipients) and foetal distress syndrome (1.8% in vaccine recipients vs. 1.6% in placebo recipients). There were 28 cases of premature delivery in the vaccine group (0.8%) and 23 cases in the placebo group (0.6%). Four serious adverse events (pain in the arm followed by bilateral lower-extremity pain, premature labour, systemic lupus erythematosus, and eclampsia) were reported in one vaccine recipient each. Additionally, one serious adverse event (premature placental separation) was reported in one placebo recipient. All serious adverse events were assessed by the investigator as being related to the injection. The incidence of serious adverse events in infants reported through 24 months was reported as similar between the groups, with no events considered by the investigators as related to the vaccine. One maternal recipient of the vaccine died

from postpartum haemorrhage and hypovolemic shock. Stillbirth occurred in 10 participants of the vaccine group and eight participants of the placebo group. Spontaneous abortion during a subsequent pregnancy occurred in one participant of the vaccine group and two participants of the placebo group. There were a reported 17 deaths in infants and toddlers from birth through 24 months of age (five in the vaccine group and 12 in the placebo group).

Summary of evidence appraisals of the maternal vaccine conducted by identified countries

The following observations were noted by countries that included an evidence summary or evaluation of clinical trial results pertaining to the maternal vaccine:

- Following GRADE methodology, the overall quality of evidence was judged as high quality in a rapid review conducted by the Belgian KCE.[127]
    - The authors of the KCE report noted that the results are from an interim analysis, and as such, the overall evidence quality could be downgraded to moderate quality until the final results are published.
    - The outcome of vaccine efficacy against severe medically-attended RSV-associated LRTI was judged by the KCE as high quality, although the authors noted that the wide confidence intervals (vaccine efficacy 81.8% (99.5% CI: 40.6 to 87.1) at 90 days of life and 69.4% (97.58% CI: 44.3 to 84.1) at 180 days of life) could merit downgrading to moderate quality of evidence.
    - The outcome of vaccine efficacy against RSV-associated hospitalisation was downgraded by the KCE to moderate quality of evidence due to imprecision (vaccine efficacy 67.7% (99% CI: 15.9 to 89.5) at 90 days and 56.8% (99% CI: 10.1 to 80.7) at 180 days).
- In presentations to the ACIP in June 2023 and September 2023, the NCIRD in the US judged the overall quality of evidence, as per GRADE methodology, as very low.[128-130]
    - The maternal vaccine was considered by the NCIRD to be effective at preventing medically-attended RSV-associated LRTI (high certainty of evidence) and at preventing hospitalisation for RSV-associated LRTI (moderate certainty of evidence). The latter outcome was downgraded for imprecision due to the width of the confidence intervals.
    - The NCIRD noted that the maternal vaccine may be effective at preventing ICU admission and mechanical ventilation resulting from

RSV-associated hospitalisation (low certainty of evidence). This outcome was downgraded twice for imprecision due to the width of the confidence intervals.

- The NCIRD considered that the maternal vaccine was not effective at preventing all-cause medically attended LRTI (moderate certainty of evidence). This outcome was downgraded for imprecision due to the width of the confidence intervals.
- The maternal vaccine was considered by the NCIRD to be effective at preventing all-cause hospitalisation for LRTI (moderate certainty of evidence). This outcome was downgraded for serious concern of imprecision due to the width of the confidence intervals.
- The NCIRD noted that data on the critical harm outcome of preterm birth showed an imbalance between the vaccine and placebo groups, with more preterm births in the vaccine group (very low certainty of evidence). This outcome was downgraded twice for serious concern of imprecision due to the width of the confidence intervals and not meeting size requirements. It was additionally downgraded for indirectness since the FDA-approved administration interval is 32 to 36 wGA, whereas the trial interval was 24 to 36 wGA.
- Data on the important harm outcome of reactogenicity (grade three or higher) was noted by the NCIRD to show balanced events between vaccine and placebo groups (moderate certainty of evidence). This outcome was downgraded for serious concern of indirectness as local events were not reported, only systemic reactions.

- The KCE and NCIRD reports noted the absence of data on RSV-related mortality.[127, 129]
- Reports from Ireland and the Netherlands noted concerns regarding a potential association between maternal vaccination against RSV and preterm births.[11, 121]
  - In the MATISSE trial, the incidence of preterm births in the vaccine group was 0.8% (n=28 cases) and in the placebo group was 0.6% (n=23 cases).[125] In February 2022, a trial investigating maternal vaccination with another vaccine against RSV, manufactured by GlaxoSmithKline, was halted due to a safety signal concerning increased preterm births among the vaccinated cohort.[131] This prompted a further review of data from the MATISSE trial. There was no difference between the trial arms in terms of the proportion

experiencing preterm births (defined as less than 37 wGA) in high-income countries. The difference in preterm births was more prominent in upper-middle income countries (7.5% in the vaccine group, 4.1% in the placebo group). The largest imbalance in preterm births between trial groups was observed in data from South Africa (8.3% in the vaccine group, 4% in the placebo group). The reason for this imbalance was unclear.

- It was noted that in the MATISSE trial, populations at higher risk of preterm delivery were excluded from the trial. In addition, rates of preterm delivery in the trial population were below the background rates, leading to concerns that the trial may have been underpowered to detect a significant increase in preterm births.
- The EMA has authorised the administration of the maternal vaccine between 24 and 36 wGA.[9] The US Food and Drug Administration (FDA) has advised a restricted administration window, between 32 and 36 wGA.[132] In Belgium, a preferential administration window between 28 and 36 wGA is recommended.[65] In Norway, while administration is recommended between 24 and 36 wGA, the Institute of Public Health noted that the best effects appear to be between 30 and 36 wGA.[88]

- In the Netherlands, the Standing Committee on Vaccinations made several observations on the vaccine efficacy findings of the MATISSE trial, noting that:[133]
  - maternal vaccination may be less effective for infants born after the RSV season, as after six months the efficacy of the vaccine decreases against RSV infection requiring medical attendance (from 51% (98% CI: 29 to 67) at 6 months to 41% (99% CI: 16 to 59) at 12 months) and against hospitalisation due to RSV infection (from 57% (99% CI: 10 to 81) at 6 months to 33% (99% CI: -18 to 63) at 12 months).
  - vaccine efficacy against medically-attended serious RSV infection was high up to six months after birth at 69.4% (98% CI: 44.3 to 84.1).
  - there is uncertainty regarding the efficacy of the maternal vaccine against hospitalisation due to RSV infection, given the wide confidence intervals at six months and 12 months after birth.

3.4 Summary of international practice for the immunisation of older adults

This section summarises the recommendations of EU/EEA countries and the UK with respect to the use of authorised RSV vaccines as preventive measures against RSV infection in older adults. Additional information regarding funding of these vaccines and their implementation as part of an immunisation programme is also summarised, where available. It should be noted that, while the target population for this rapid HTA is adults aged 65 years and older, information identified for some countries applies to groups outside the target population (for example, adults aged 60 years and older).

3.4.1 Recommendations on the use of RSV vaccines in older adults

The search by HIQA'S evaluation team identified 16 countries with information relating to the use of RSV vaccines in older adults. Recommendations were identified for six countries: Austria, Belgium, Ireland, Norway, Sweden and the UK. Assessments or evaluations of vaccines for older adults were reported to be in progress in four countries: France, Germany, Ireland and Spain. For six countries (Czech Republic, Denmark, Finland, Iceland, Netherlands and Portugal), the identified information indicated that RSV vaccines were available to older adults, but no recommendations on vaccination were identified. Where information on recommendations, implementation as part of an immunisation programme, and or funding of RSV vaccines for older adults was identified, a brief summary is provided below. A brief overview for all included countries is provided in Table 3.3, while more detailed summaries for each country are provided in Appendix 3A Table 2.

Austria

According to the Austrian Vaccination Plan 2023-2024, vaccination with an approved RSV vaccine is recommended for adults aged 60 years and older.[134] In addition, off-label use of RSV vaccines can be considered for adults aged 18 years and older with risk factors for increased risk of illness, listed in Appendix 3A Table 2. Vaccination is available at a cost to the individual, as the vaccines are not funded as of 1 July 2024.

Belgium

In September 2023, the Superior Health Council (SHC) in Belgium published recommendations on vaccination of older adults against RSV.[135] According to the guidance, RSV vaccination can be offered on an individual basis to adults aged 60 years and older with at least one risk factor of severe RSV disease (see Appendix 3A Table 2). The evidence that informed this recommendation included consideration of the epidemiology and burden of RSV in Belgium, and internationally, as well as the clinical efficacy and safety evidence for the two authorised RSV vaccines. Factors supporting vaccination included the high morbidity and mortality associated with RSV

infection among older adults with risk factors for serious disease and the lack of effective anti-viral therapy options. However, the Council noted that the data available on vaccine efficacy for severe outcomes was limited, especially in frail older adults. The GRADE framework was used to evaluate evidence quality for the RSVPreF3 (Arexvy®) vaccine. The overall certainty of evidence for its efficacy was determined to be moderate to low. RSV vaccines were not funded in Belgium as of 1 July 2024.[136]

Czech Republic

As of 1 July 2024, RSV vaccines are available, on an individual basis, for adults aged 60 years or older at certain hospitals.[137] Vaccination is not fully funded, but individual insurance companies, including the country's largest health insurance company, provide partial contributions.[138]

France

As of 1 July 2024, an assessment of the vaccination of older adults against RSV is being undertaken by HAS.[139] The assessment includes all adults aged 65 years and older regardless of risk, and adults aged between 60 and 64 years with risk factors for complications resulting from RSV infection. A decision is expected in July 2024.

Germany

As of 1 July 2024, the STIKO are evaluating RSV prevention options, with its comments expected to be published by summer 2024.[140] In June 2024, a preprint journal article was posted online reporting on a modelling study of different RSV immunisation strategies for Germany, developed in consultation with the working group of RSV at STIKO.[141] Vaccination of older adults with an RSV vaccine (administered from October to February) was modelled for those aged 55 years and older, 65 years and older, and 75 years and older. Each vaccination strategy was modelled in addition to providing nirsevimab to all infants aged one to five months (administered from November to March). The comparator was no adult vaccination and only immunisation of infants aged one to five months with nirsevimab. Uptake was assumed to be 70% for nirsevimab and 40% for adult vaccination. The authors noted that vaccination of older adults could prevent considerable disease burden, but the precise extent of RSV burden averted in older adults by vaccination is not well defined, as the true burden of RSV is underestimated in older adults. The findings from this modelling study are expected to inform STIKO's ongoing assessment of RSV immunisation options.

Ireland

In October 2023, NIAC recommended vaccination for adults aged 65 years or older with either RSVPreF3 (Arexvy®) or RSVpreF (Abrysvo®).[11] However, NIAC also recommended that a further analysis of costs and product availability is needed to determine the most suitable product for use in Ireland. Groups to be prioritised, in case of limited vaccine supply, were those at high risk of RSV disease, namely older adults of more advanced age, those with significant comorbidities, and older adults living in long-term care facilities. NIAC also noted that the recommendations may be updated if more information becomes available. HIQA was requested by the Department of Health to undertake this rapid HTA to inform a policy decision regarding funding.

Norway

Recommendations from the Norwegian Institute of Public Health stated that the RSV vaccine can be considered for adults aged 60 years and older with an underlying disease. As of 1 July 2024, RSV vaccines are available to be ordered from the Institute of Public Health or from a pharmacy, but are not implemented as part of an immunisation programme and are not funded.[88]

Spain

No national recommendation regarding vaccination of older adults against RSV was identified. As part of recommendations for infant immunisation for the 2023-2024 RSV season,[142] and the 2024-2025 season,[122] the Public Health Commission stated that recommendations and target groups for RSV prevention strategies would be reviewed for subsequent RSV seasons. A working group was established to evaluate potential immunisation programmes for children and adults, including consideration of both available and soon-to–be-authorised vaccines. The Ministry of Health also requested an evaluation from the Spanish Network of Health Technology Assessment Agencies and Benefits of the National Health System (RedETS) to include a systematic review of the scientific evidence on the effectiveness, safety and efficiency of immunisation against RSV, as well as an economic analysis.[122] Expected dates of completion for these evaluations were not identified.

Sweden

For the 2023-2024 RSV season, the Swedish Public Health Agency recommended vaccination against RSV for adults aged 75 years or older, and adults aged 60 years or older with certain risk factors (see Appendix 3A Table 2).[143] The Agency noted that recommendations may change for the 2024-2025 season. As of 1 July 2024, both RSV vaccines are available for individuals to purchase, but are not included as part of an immunisation programme and are not funded.[144, 145]

United Kingdom

In June 2024, the UK Health Security Agency published correspondence detailing the introduction of two new nationally-funded NHS vaccination programmes against RSV: one for the immunisation of infants through maternal vaccination during pregnancy and one for the vaccination of older adults.[103] From 1 September 2024, all adults turning 75 years old on or after that date will be eligible for a single dose of RSV vaccine (RSVpreF – Abrysvo®) as part of the routine RSV vaccination programme.[103] From 1 September 2024, all adults turning 75 years old on or after that date will be eligible for a single dose of RSV vaccine (RSVpreF – Abrysvo®) as part of a routine RSV vaccination programme. A one-off catch-up campaign will run between 1 September 2024 and 31 August 2025, for people aged 75 to 79 years. Individuals will remain eligible until the day before their 80th birthday, with the exception of people who turn 80 in the first year who have until 31 August 2025 to get vaccinated.

Table 3.3 Summary of practices with respect to immunisation against RSV in older adults in EU/EEA countries and the UK, as of 1 July 2024

Country	Recommended	Available	Funded	Part of an immunisation programme
Austria	✓	✓	X	✓
Belgium	✓	✓	X	X
Bulgaria	N/I	N/I	X	N/A
Croatia	N/I	N/I	N/A	N/A
Cyprus	N/I	N/I	N/A	X
Czech Republic	N/I	✓	✓±	X
Denmark	X	✓	X	X
Estonia	N/I	N/I	N/A	X
Finland	X	✓	X	X
France	X*	N/I	N/A	N/A
Germany	X*	✓	X	X
Greece	N/I	N/I	N/A	X
Hungary	N/I	N/I	N/A	N/A
Iceland				

Country	Recommended	Available	Funded	Part of an immunisation programme
RSVpreF (Abrysvo®)	N/I	✓	X	X
RSVPreF3 (Arexvy®)	N/I	N/I	X	X
Ireland	✓*	✓	X	X*
Italy				
RSVpreF (Abrysvo®)	N/I	✓	X*	X
RSVPreF3 (Arexvy®)	N/I	✓	X	X
Latvia	N/I	N/I	N/A	X
Liechtenstein	N/I	N/I	N/A	N/A
Lithuania	X	N/I	N/A	N/A
Luxembourg	X	✓	X	N/A
Malta	N/I	N/I	N/A	N/A
Netherlands	X	✓	X	N/A
Norway	✓	✓	X	X
Poland	N/I	N/I	N/A	N/A
Portugal	N/I	✓	X	N/A
Romania	N/I	N/I	N/A	N/A
Slovakia	N/I	N/I	N/A	X
Slovenia	N/I	N/I	N/A	N/A
Spain	X*	✓	N/I	X
Sweden	✓	✓	N/I	X
United Kingdom				
RSVpreF (Abrysvo®)	✓	✓	✓	✓
RSVPreF3 (Arexvy®)	✓	X	X	X

Key: N/A – not applicable; N/I – no information identified.
Unless otherwise stated, information refers to the RSV vaccines authorised by the European Medicines Agency; as of 1 July 2024, these are: RSVpreF (Abrysvo®) and RSVPreF3 (Arexvy®).
* Ongoing assessment, as of 1 July 2024.
± Eligible for partial funding through health insurance.

3.4.2 Summary of the clinical trials that informed countries' recommendations for older adults

RSVPreF3 (Arexvy®)

AReSVi-006 phase 3 trial

The Adult Respiratory Syncytial Virus (AResVi-006) phase 3 RCT recruited adults aged 60 years or older to receive either a single dose of an $AS01_E$-adjuvanted RSV prefusion F protein-based candidate vaccine (RSVPreF3 OA) or placebo before the start of the RSV season.[42] The primary objective of this trial was to evaluate the efficacy of a single dose of the vaccine at preventing RSV-associated lower respiratory tract disease (LRTD) (as confirmed by reverse transcriptase polymerase chain reaction (RT-PCR)) during one RSV season.[146] RSV-associated mortality was not evaluated.

In February 2023, a prespecified interim efficacy analysis was published which included a total of 24,960 patients in the modified exposed population (that is, those who received the vaccine or placebo and did not report an RSV-associated acute respiratory infection before day 15 after injection).[42] Vaccine efficacy against RSV-associated LRTD was estimated at 82.6% (96.95% CI: 57.9 to 94.1) based on a median follow up of 6.7 months (vaccine group n=7/12,466; placebo group n=40/12,494). Vaccine efficacy was also reported against severe RSV-associated LRTD (VE: 94.1% [95% CI: 62.4 to 99.9]) and RSV-associated acute respiratory infection (VE: 71.7% [95% CI: 56.2 to 82.3]). Vaccine efficacy for RSV-associated LRTD was also reported stratified by age (VE: 81.0% [95% CI: 43.6 to 95.3] and VE: 93.8% [95% CI: 60.2 to 99.9]) for adults aged 60 to 69 years and 70 to 79 years, respectively. As part of its recommendations for the US, the ACIP cited further unpublished efficacy data provided by the manufacturer for a second complete RSV season in the Northern Hemisphere. The mean follow-up time per participant was 15.3 months. The efficacy of one dose of the vaccine in preventing symptomatic, laboratory-confirmed RSV-associated LRTD was 56.1% (95% CI: 28.2 to 74.4) during the second season. The efficacy of one dose over two seasons was 74.5% (97.5% CI: 60.0 to 84.5).[147]

Typically, solicited adverse events and reactions (that is, an event that was pre-specified and recorded by participants as it occurred) were more common among the vaccine group compared with the placebo group. The most common solicited injection-site reaction was pain (vaccine group 60.9% (95% CI: 57.5 to 64.1); placebo group 9.3% (95% CI: 7.4 to 11.4)) and the most common solicited systemic reaction was fatigue (vaccine group 33.6% (95% CI: 30.4 to 36.8); placebo group 16.1% (95% CI: 13.7 to 18.7)). In this solicited safety population, the incidence of unsolicited adverse events (that is, other symptoms that occurred within 30 days after injection) was similar between the two groups (vaccine group 14.9%; placebo group 14.6%). Additional unsolicited safety outcomes were reported for the exposed

population (total n=24,966) that received either vaccine or placebo. From 22,666 participants (90.8%) for whom six months of follow-up data were available, there was no difference in the risk of serious adverse events (4.2% vs. 4.0%; relative risk 1.03 [80% CI: 0.95 to 1.12]). There were 10 vaccine recipients (0.1%) and seven placebo recipients (0.1%) who had a serious adverse event that was considered related to vaccine or placebo. A total of 49 vaccine recipients (0.4%) and 58 placebo recipients (0.5%) died. Three fatal serious adverse events were considered by the investigators to be related to vaccine or placebo administration (group assignment blinded).

Phase 1/2 safety trial (NCT03814590)

This phase 1/2 RCT investigated the safety and immunogenicity of RSVPreF3 vaccine formulations against RSV.[148] Those enrolled included 1,005 older adult participants aged 60 to 80 years. For these older adults, participants were randomised to receive either unadjuvanted vaccine at one of three different RSVPreF3 antigen concentrations (30µg, 60µg, or 120µg), AS01-adjuvanted vaccine (either $AS01_E$ or $AS01_B$, at one of the three RSVPreF3 antigen concentrations) or placebo. For each of the nine vaccine groups and the placebo group, two doses were administered two months apart. Vaccine safety and immunogenicity were assessed until 12 months after second vaccination in older adults.

This summary is restricted to safety results for the older adult cohort relating to the formulation authorised by the EMA (that is, 120µg RSVPreF3 antigen with $AS01_E$ adjuvant). In the older adult cohort, 1,005 participants received at least one dose of vaccine or placebo and 970 participants received two doses. Solicited adverse events were more frequent in the vaccine compared with the placebo group. The most frequently reported injection-site adverse event was pain (65.0% vs. 8.0% in the vaccine and placebo groups). Grade three solicited adverse events occurred in the vaccine group (2.0% to 3.0%) but not in the placebo group. Within 30 days after vaccination, proportions of unsolicited adverse events were similar between groups. No serious adverse events were considered vaccine-related. One vaccine participant was withdrawn due to a serious adverse event or potential immune-mediated diseases (pIMD). No deaths were reported. Two pIMDs (Bell's palsy (60µg) and rheumatoid arthritis (120µg)) were reported in the vaccine group, neither of which were considered vaccine-related.

RSVpreF (Abrysvo®)

RENOIR phase 3 trial

This phase 3 RCT evaluated the efficacy and safety of RSVpreF vaccine in preventing RSV-associated LRTD during the first RSV season after injection.[149] Adults aged 60

years and older were recruited to receive either one dose of unadjuvanted RSVpreF vaccine or placebo. The first primary end point was the efficacy of RSVpreF vaccine in preventing RSV-associated LRTD with at least two signs or symptoms lasting more than one day and confirmed by means of RT-PCR (or by nucleic acid amplification test if RT-PCR was unavailable) within seven days after onset of signs or symptoms.[150]

In April 2023, a prespecified interim efficacy analysis was published after 44 cases (vaccine group n=11; placebo group n=33) of RSV-associated LRTD with at least two signs or symptoms had occurred.[149] A total of 34,484 participants (vaccine group 17,215; placebo group 17,069) received RSVpreF vaccine or placebo. The vaccine efficacy against RSV-associated LRTD with at least two signs or symptoms was 66.7% (97% CI: 28.8 to 95.8), which met the primary objective. There were 16 cases of RSV-associated LRTD with at least three signs or symptoms (vaccine group n=2; placebo group n=14), corresponding to a vaccine efficacy of 85.7% (95% CI: 32.0 to 98.7). As part of its recommendations for the US, the ACIP cited further unpublished efficacy data provided by the manufacturer for a partial second season for Northern Hemisphere participants only. Mean follow-up time across both seasons, including a gap in RSV surveillance between the first and second RSV seasons, was approximately 12 months per participant. Efficacy of one dose of the vaccine in preventing symptomatic, laboratory-confirmed RSV-associated LRTD was 78.6% (95% CI: 23.2 to 96.1) during the partial second season. Efficacy of a single dose over two seasons was 84.4% (95% CI: 59.6 to 95.2).[147]

There were more local reactions reported by those in the vaccine group compared with the placebo group (12% and 7%, respectively). The incidence of systemic events was similar between groups (vaccine group 27%; placebo group 26%). At the time of the interim analysis, a similar proportion of serious adverse events were reported between groups (vaccine group 2.3%; placebo group 2.3%). Three serious adverse events in the vaccine group were considered related to the vaccine. No trial intervention-related deaths or adverse events leading to withdrawal from the trial were reported.

Phase 1/2 safety trial (NCT03529773)

This phase 1/2 RCT investigated the safety and immunogenicity of vaccine formulations against RSV administered alone or concomitantly with seasonal inactivated influenza vaccine (SIIV).[151] While a range of RSVpreF vaccine doses (60µg, 120µg or 240µg) and formulations (with and without aluminium hydroxide adjuvant) were investigated in this trial, where possible, this summary focuses on the results for the older age group (65 to 85 years), randomised to receive a single

dose of placebo or a single dose of the formulation of RSVpreF vaccine ultimately authorised by the EMA (that is, 120µg without adjuvant).

There were 122 participants randomised in the cohort aged 65 to 85 years, to receive either placebo (n=41), RSVpreF 120µg without adjuvant (n=40) or RSVpreF 120µg without adjuvant with SIIV (n=41). Of these participants, two in the placebo group did not complete 12-months follow up (adverse event n=1; loss to follow-up n=1) so that safety results were reported for 120 participants. One participant randomised to the 120µg RSVpreF with SIIV group was instead administered a higher dose with adjuvant, but was included in the group to which they were randomised. Any local or systemic adverse event was experienced by 20% (n=8/40) of participants in the 120µg RSVpreF group, 22.5% (n=9/41) of those in the RSVpreF 120µg with SIIV group, and 12.2% (n=5/39) participants in the placebo group. Serious adverse events through 12 months post-vaccine were reported by 5% (n=2/40) of the 120µg RSVpreF group, 10% (n=4/40) of the 120µg RSVpreF with SIIV group, and 7.3% (n=3/39) in the placebo group. Across all groups, no serious adverse events were considered to be vaccine-related. Medically-attended adverse events (MAEs) through 12 months post-vaccine were reported by 22.5% (n=9/40) of participants in the 120µg RSVpreF group, 22.5% (n=9/41) of the RSVpreF 120µg with SIIV group and 14.6% (n=6/39) in the placebo group.

Phase 1/2 safety trial (NCT03572062)

This phase 1/2 trial evaluated the safety and immunogenicity of different RSVpreF vaccine formulations (with and without adjuvants) at a range of different dose levels in healthy older adults when co-administered with a high-dose trivalent seasonal inactivated influenza vaccine.[152] Notably, none of the vaccine dosages or formulations evaluated in this trial were the same as the RSVpreF vaccine authorised by the EMA (that is, 120µg without adjuvant). The safety data from this trial were therefore not considered directly relevant to this assessment.

Summary of evidence appraisals relating to RSV vaccines in older adults by identified countries

RSVPreF3 (Arexvy®)

In Belgium, the SHC considered the overall certainty of evidence to be moderate to low, using the GRADE approach.[135] This was based solely on interim results from the AReSVi-006 trial.[42]

- The evidence was downgraded by the SHC by one level due to indirectness, as the majority of trial participants were relatively young (aged less than 70 years) and at lower risk of severe RSV disease than the general population of

adults aged 60 years or older. For example, individuals with immunosuppression or unstable co-existing health conditions were excluded from participating in the trial, and approximately 70% of participants in each group had no co-existing conditions at baseline.

- The SHC report acknowledged that downgrading by one more level could have been justified, since interim results from only one trial were presented and critical outcomes such as mortality rate or hospitalisation rate were not reported.

NIAC recommendations for Ireland referred to the evidence appraisal conducted by the NCIRD to inform the ACIP's recommendations for the US.[11] The NCIRD described the available evidence as ranging from high certainty to very low certainty, using the GRADE approach.[153] This was based on results from the phase 3 AReSVi-006 trial and one phase 1/2 trial.[42, 148]

- The initial GRADE evidence level was considered by the NCIRD to be high for each outcome since the evidence consisted of randomised controlled trials.
- In terms of efficacy against RSV LRTD and medically attended LRTD, the evidence was downgraded by the NCIRD to moderate certainty due to indirectness. Similar to the SHC's evaluation, this was due to the age profile of participants and the exclusion of individuals with immunosuppression.
- Evidence of efficacy against hospitalisation for RSV respiratory illness and severe RSV respiratory illness requiring supplemental oxygen or other respiratory support was downgraded by the NCIRD to very low certainty due to indirectness and imprecision.
- Estimates for serious adverse events or severe local or systemic reactions were both considered to be of high certainty by the NCIRD.
- In terms of safety, the NCIRD noted that certainty could not be assessed in relation to inflammatory neurologic events, since no such events were recorded in the phase 3 trial of the RSVPreF3 (Arexvy®) vaccine. However, three events were recorded in trials excluded from GRADE due to the lack of an unvaccinated comparator arm. These events occurred in three of 17,922 participants within 42 days after receiving the vaccine. The reported cases included one case of Guillain-Barré syndrome (GBS) and two cases of acute disseminated encephalomyelitis (ADEM). Uncertainty in the diagnoses of both ADEM cases was reported, because diagnosis was based on symptoms and clinical findings only, with no diagnostic testing conducted. For one of the ADEM cases, the investigator revised the diagnosis to hypoglycaemia and

dementia in June 2023.[153] These adverse events were also noted in the NIAC recommendations for Ireland.[11]

RSVpreF (Abrysvo®)

NIAC recommendations for Ireland referred to the evidence appraisal conducted by the NCIRD to inform the ACIP's recommendations for the US.[11] The NCIRD described the available evidence as ranging from high certainty to very low certainty, using the GRADE approach.[130] This was based on results from the RENOIR phase 3 trial and one phase 1/2 trial.[149, 151]

- The NCIRD considered that the initial GRADE evidence level was high for each outcome because the evidence consisted of randomised controlled trials.
- In terms of efficacy against RSV LRTI and medically attended LRTI, the evidence was downgraded by the NCIRD to moderate certainty due to indirectness. Similar to the evidence relating to RSVPreF3 (Arexvy®), this was due to the age profile of participants and the exclusion of individuals with immunosuppression.
- Evidence of efficacy against hospitalisation for RSV respiratory illness and severe RSV respiratory illness requiring supplemental oxygen or other respiratory support were both downgraded by the NCIRD to very low certainty due to indirectness and imprecision.
- Estimates for serious adverse events were considered by the NCIRD to be of high certainty.
- Estimates for severe local or systemic reactions following vaccination was considered by the NCIRD to be of moderate certainty, having been downgraded due to imprecision.
- For inflammatory neurologic events, the evidence was downgraded by the NCIRD to low certainty due to imprecision. Across all clinical trials, inflammatory neurologic events were reported in three of 20,255 participants within 42 days after receiving the vaccine. These events included one case of GBS, one case of Miller Fisher syndrome, and one case of undifferentiated motor-sensory axonal polyneuropathy with worsening of pre-existing symptoms.

General observations on RSV vaccines

In February 2024, early post-licensure safety monitoring data relating to RSV vaccines in adults aged 60 years and older were presented at a meeting of the ACIP

in the US.[154] Updates were presented from several monitoring sources, such as V-safe, the Vaccine Adverse Reporting System (VAERS), and the Vaccine Safety Datalink (VSD). While initial results were subject to the limitations of passive surveillance (VAERS), early data from these various systems (VAERS, VSD) suggest the potential for an increased rate of Guillain-Barré syndrome (GBS) after RSV vaccination. As such, the CDC and FDA have indicated that they will continue to monitor RSV vaccine safety. It was noted that GBS cases were observed in the pre-licensure clinical trials for both RSV vaccines and GBS is included as an adverse event in the labels of both vaccines.[154] It was noted that GBS cases were observed in the pre-licensure clinical trials for both RSV vaccines, and GBS is included as a potential adverse event in the labels of both vaccines.[154]

In the UK, the JCVI noted in their September 2023 report that data relating to the RSVPreF3 (Arexvy®) vaccine suggested that it might have a better efficacy than the RSVpreF (Abrysvo®) vaccine, but there was uncertainty in comparing the vaccines, as there were no head-to-head studies. Furthermore, it noted that the respective clinical trials for each vaccine used different case definitions and end points, and different measurement methods.[102]

The JCVI also noted that there were no major safety concerns in relation to the vaccines at the time of publishing their advice.[102] However, the Public Health Agency in Sweden noted that current safety data related to a relatively small sample of participants, and surveillance following widespread implementation of RSV vaccines was required.[143]

3.5 Discussion

A review was undertaken of immunisation practices in 31 EU/EEA countries and the UK, which considered recommendations regarding RSV immunisation strategies for infants and older adults, the inclusion of strategies within national immunisation programmes and immunisation funding decisions. Differences were noted among countries in terms of decision making processes. For some countries, recommendations with respect to immunisation policy are made by National Immunisation Technical Advisory Groups (NITAGs) based on clinical burden and evidence of effectiveness and safety. Some NITAGs also explicitly consider cost effectiveness; however, in other countries, economic considerations are informed by advice from HTA bodies. Policy decisions regarding funding may be automatic following a positive recommendation or advice from a NITAG or HTA body, or it may be the case that, as in Ireland, the final decision is made by the Minister for Health or a representative body. While recommendations were identified for multiple countries, it was not always clear if a policy decision had also been made to fund the strategy in question or if this funding decision was implicit. Internationally, decision-

making regarding RSV immunisation is further complicated by the fact that the monoclonal antibodies, nirsevimab and palivizumab, are not vaccines. The remit of some NITAGs is limited to vaccines, with responsibilities for non-vaccine medicinal products, such as the monoclonal antibodies, lying with other agencies.

3.5.1 Immunisation of infants

Overall, as outlined in Table 3.2, current infant immunisation practices varied across the included countries.

Infants at high risk of severe disease

In all 31 countries included in this review, palivizumab is recommended, available or can be considered for the prevention of serious RSV-associated disease, and it is funded (fully or partially) in 19 countries. However, there is some variation in the populations for which it is recommended and or funded. These variations primarily relate to the gestational age at which infants are born and their age during the RSV season. For example, in Belgium, palivizumab is recommended and funded for infants born at less than or equal to 28 wGA and aged less than one year at the start of the RSV season, whereas in Germany, it is recommended and funded for infants born at less than 35 wGA and aged less than six months at the start of the RSV season.

While practices relating to the use of palivizumab for infants at high risk of severe disease are well established, current practices relating to the use of nirsevimab primarily related to the 2023-2024 RSV season. A limited number of countries have published information for the 2024-2025 RSV season or future seasons, and a number of countries are in the process of updating their practices at the time of conducting this review. For example, between April and July 2024, a recommendation for immunisation of all infants in their first RSV season was published in Germany,[72] updated practices in relation to funding of nirsevimab for the 2024-2025 RSV season were announced in Belgium[67] and France,[69] and a temporary publicly-funded programme to implement immunisation with nirsevimab was announced in Ireland.[12] Such changes are indicative of the considerable flux in international practices at the time of conducting this rapid HTA and the likelihood that further updates will occur ahead of the 2024-2025 season.

Infants in the general population - recommendations

Ten countries currently recommend or advise universal immunisation of newborns and young infants (that is, immunisation of all children before or during their first RSV season, including children at high risk of severe RSV disease). One of these countries (Germany) initially recommended and funded immunisation of infants at high risk of severe RSV disease only (such as those born preterm or with risk factors

for severe disease). This was in line with the remit of the Federal Joint Committee (G-BA). A decision to fund immunisation for those without defined risk factors could only be made following a positive recommendation from the Standing Committee on Vaccination (STIKO), the German NITAG, which was published in June 2024. Four of the ten countries that recommend universal immunisation with nirsevimab (Germany, Ireland, Spain and Sweden) include priority groups for immunisation in their recommendations, particularly in the case of limited supply, with groups at higher risk of severe RSV disease being of higher priority. For the 2023-2024 RSV season, three countries implemented nirsevimab as part of a publicly-funded national immunisation programme (France, Luxembourg and Spain), and it was available for eligible infants in Germany. In addition, for the 2024-2025 season, nirsevimab is expected to be available as part of a pilot national immunisation programme in Ireland. In Austria, Belgium and Sweden, nirsevimab is not currently available, but it is expected to become available during 2024. Finally, although nirsevimab is not yet recommended in Norway, the Norwegian Association of Paediatricians plan to recommend it once it becomes available, subject to price.[155] The findings of this review align with those of a scoping review, published in February 2024, on the use of preventive tools against RSV for neonates and infants in Europe.[156]

In the limited number of countries that recommend the maternal vaccine or recommend that its use be considered for pregnant women, there is variation in the recommended window for vaccination. In five countries, it is available for pregnant women between 24 and 36 wGA, in line with its EMA authorisation. Narrower windows for vaccination are recommended in Belgium (between 28 and 36 wGA), the UK (between 28 wGA and delivery), France and Luxembourg (both between 32 and 36 wGA, which is in line with the US FDA's advised vaccination window). The maternal vaccine is only eligible for funding in three of the 14 countries where it is available: the UK and Spain (both fully funded) and the Czech Republic (partially funded). In Ireland, the maternal vaccine was recommended by NIAC in October 2023 but was not included in NIAC's April 2024 recommendations for the 2024-2025 season. In the UK, the maternal vaccine is recommended and planned to be implemented as part of an immunisation programme from 1 September 2024, and has been proposed for recommendation and inclusion in an immunisation programme in Slovenia. In the Netherlands, the Vaccinations Committee of the Health Council advised offering nirsevimab instead of the maternal vaccine, while in Luxembourg, either nirsevimab or the maternal vaccine are recommended for the 2024-2025 season, according to the choice of parents and healthcare providers. In Italy, both nirsevimab and the maternal vaccine are currently being evaluated for funding. In addition, assessments of RSV preventive options, including use of the maternal vaccine, are ongoing in three countries (Germany, Spain and Sweden).

Infants in the general population – funding decisions

For the general infant population, five countries (Belgium, France, Germany, Spain and the UK) have immunisation programmes planned or in place for the 2024-2025 RSV season. The programmes vary in terms of the method of immunisation (that is, use of nirsevimab and or the maternal vaccine), eligibility, the defined timing and duration of the RSV season, and priority groups for immunisation (for example, in the event of limited supply. Of the five countries (Belgium, France, Germany, Spain and the UK) with publicly-funded immunisation programmes planned or in place for the 2024-2025 RSV season, four countries (Belgium, France, Germany and Spain) preferentially recommend nirsevimab in place of palivizumab for infants and children at increased risk of RSV disease. In the UK, infants and children at increased risk of RSV disease will be offered passive immunisation with palivizumab, regardless of whether the mother was vaccinated during pregnancy.

Infants in the general population – evidence base

The evidence that underpinned a decision to recommend passive immunisation of infants through the administration of nirsevimab or maternal vaccination largely consisted of results from five industry-sponsored clinical trials. The evidence base for nirsevimab consisted of three RCTs investigating efficacy and safety (D5290C00003, MELODY and HARMONIE), an additional RCT investigating safety (MEDLEY), and a fifth open-label trial investigating safety in immunocompromised children (MUSIC). Nirsevimab was considered likely to be effective at preventing medically attended RSV-associated LRTI and RSV-associated LRTI hospitalisations among infants in their first year of life, with high certainty of evidence as assessed by agencies in Belgium and the US.[114-117] Countries noted concerns about the limited data on the impact of nirsevimab on ICU admissions and the absence of data on mortality. In addition, it was highlighted that clinical data supporting the use of nirsevimab in patients eligible to receive palivizumab is limited, and there are no direct comparison trials of nirsevimab with palivizumab in such infants.

For the maternal vaccine, the clinical efficacy and safety evidence considered by countries was derived primarily from one RCT (MATISSE). The maternal vaccine was considered likely to be effective at preventing medically attended RSV-associated LRTI and RSV-associated LRTI hospitalisations among infants, with moderate to high certainty of evidence for these outcomes. Countries noted concerns about the absence of data on RSV-related mortality, and uncertainty regarding the potential effect of the maternal vaccine at reducing RSV-related ICU admissions. The Standing Committee on Vaccinations in the Netherlands noted the wide confidence intervals associated with vaccine efficacy for non-severe RSV-associated LRTI. The committee suggested that six months after vaccination the efficacy is insufficient, and infants born in the spring may not be adequately protected during their first RSV season. In addition, there were concerns regarding the potential association between maternal

vaccination against RSV and preterm births, and that the MATISSE trial may not have been sufficiently powered to detect a significant increase in preterm births. While the administration window authorised by the EMA is between 24 and 36 wGA, given the potential risk of preterm births, the US, Luxembourg and France have advised a restricted administration window between 32 and 36 wGA, while Belgium recommends a preferential administration window between 28 and 36 wGA. In the UK, the administration window is from 28 wGA until delivery.

The affordability, feasibility and acceptability of implementing an immunisation programme against RSV using nirsevimab and or the maternal vaccine are important considerations. In Spain, the public health commission noted that the cost-per-dose, the severity of RSV disease, the impact of the intervention on RSV-associated hospitalisations and the duration of protection are the most important parameters to be considered in cost-effectiveness evaluations. Uncertainty regarding the costs of nirsevimab and or the maternal vaccine however presents significant challenges to evaluating their cost effectiveness. While the final price paid by an organisation or country may be the subject of confidential negotiations, it is noted that nirsevimab is not yet marketed in several countries, including Ireland, so there is also uncertainty regarding the planned wholesale or list price. For example, a dossier submitted by Sanofi to inform nirsevimab funding in Finland included a list price of €700 per dose for a sample immunisation strategy.[157] However, the marketing authorisation holder provided different unit prices for other potential immunisation strategies (figures not published), and a wide range of possible unit prices were modelled in scenario analyses (discounts on the list price ranging from 0% to 90%). Moreover, it was noted that the included costs were limited to the drug cost, with no costs included for its administration. The authors reported that the models provided by the marketing authorisation holder suggested that nirsevimab would be more cost effective than palivizumab for all strategies, although these results were subject to uncertainty regarding the price and effectiveness of nirsevimab. Uncertainty regarding costs of alternative strategies is further highlighted by a 2023 economic analysis from Canada which considered costs per dose ranging between $50 and $1,000 for nirsevimab and the maternal vaccine.[158] In Spain, the Public Health Commission noted that the cost-effectiveness evidence for nirsevimab was limited, and estimates have used a price per dose as low as €50, based on other vaccines such as the rotavirus vaccine. However, it is noted that the published contract price for nirsevimab (both 50mg and 100mg vials) was €209 per dose in Galicia for the 2023-2024 season, while details of the contract price for Andalucía for the upcoming 2024-2025 season published in June 2024 was over three-fold higher, at €676.01 per dose.[159] In the Netherlands, the report by the Health Council noted that cost-effectiveness modelling studies assumed costs per dose, including administration costs, for nirsevimab of €51 to €97 and for the maternal vaccine of €51 to €92. In

contrast, the listed cost of one dose of the maternal vaccine in Belgium is €185.10 while in Germany, the cost per dose of nirsevimab listed on the Lauer Taxe database is €1,350.03. These costs per dose from Andalucía, Belgium and Germany would suggest that the cost-effectiveness modelling studies may have considerably underestimated the RSV strategy costs. Chapter 5 of this report presents a costing analysis for an RSV immunisation programme in Ireland.

Countries stressed the importance of education and information campaigns to inform healthcare providers and parents, to improve the acceptability of immunisation programmes against RSV. Factors that have previously contributed to the successful uptake of infant immunisation or antenatal vaccination should be reflected upon, and may differ by country. According to the ECDC vaccine scheduler, five countries in the EU/EEA have a general recommendation for Hepatitis B vaccination at birth, whereas 24 countries recommend vaccination at birth for specific risk groups.[160] Concerning antenatal vaccination, vaccination against pertussis is recommended in 15 countries in the EU/EEA, including Ireland. In addition, real-world evidence has started to become available from countries that have implemented immunisation with nirsevimab. Beneficial findings from such countries may help to improve perceptions of acceptability among healthcare providers and parents.

3.5.2 Immunisation of older adults

Recommendations and funding decisions

Overall, across EU/EEA countries and the UK, information on immunisation of older adults against RSV is less widely available and less detailed than information on immunisation of infants. Of the 31 countries reviewed, fewer countries had recommendations regarding the immunisation of older adults compared with the immunisation of infants. This is likely due to the more recent authorisation by the EMA of RSV vaccines (June 2023 for RSVPreF3 (Arexvy®) and August 2023 for RSVpreF (Abrysvo®)) compared with nirsevimab, which was authorised by the EMA in October 2022. Similar to the findings for immunisation practices against RSV for infants, a limited number of countries have published information for their approaches to immunisation against RSV in older adults for the 2023-2024 and or 2024-2025 RSV seasons. A summary of immunisation practices, as of 1 July 2024, against RSV in older adults among countries of the EU/EEA and the UK is provided in Table 3.3. However, it is likely that further updates will occur ahead of the 2024-2025 RSV season. To date, for countries where information on funding status was identified, it is noted that RSV vaccines are not currently publicly funded for older adults with the exception of the UK where they are fully funded as part of an immunisation programme,[103] and the Czech Republic where they are available and partially funded through insurance, but are not part of an immunisation programme.[137, 138]

Where national recommendations are in place, the groups recommended for vaccination vary to some extent among countries in terms of age and the presence of risk factors for severe RSV disease. The broadest recommendations for RSV vaccination were those identified for Austria, where RSV vaccination was recommended for the 2023-2024 season for all adults aged 60 years or older, in line with the therapeutic indications for both RSV vaccines.[10] In addition, the Austrian recommendations note that off-label use can be considered for adults aged 18 years or older with certain risk factors,[134] the only country identified to include a recommendation of this nature. In the Czech Republic, RSV vaccines are partially funded through insurance for adults aged 60 years and older.[137, 161] In three other countries (Belgium, Norway and Sweden), vaccination for adults aged 60 years or older is recommended only for those at risk of severe RSV disease (for example, individuals with certain chronic health conditions). In France, the assessment being undertaken by HAS is focused on adults aged 65 years and older regardless of risk,[139] which is in line with NIAC's recommendation for Ireland.[11] However, the HAS assessment is also considering vaccination of adults aged between 60 and 64 years at high risk of severe RSV disease. The most restrictive age-based recommendations in the countries reviewed were noted in Sweden and the UK,[102, 103, 143] where RSV vaccination is recommended for adults aged 75 years or older, with a one-off catch up campaign announced from September 2024 to August 2025 for those aged from 75 to 79 years (including those who turn 80 during this period) in the UK.

Evidence base

National recommendations on RSV vaccination for older adults have been primarily informed by the results of five clinical trials: two related to RSVPreF3 (Arexvy®)[42, 148] and three relating to RSVpreF (Abrysvo®).[149, 151, 152] In addition, further data provided by manufacturers informed the ACIP recommendations for the US,[147] which in turn informed recommendations in both Ireland and Sweden. For RSVPreF3 (Arexvy®), the overall certainty of evidence regarding its efficacy in preventing RSV LRTD was considered to be moderate[153] or moderate to low[135] by the NCIRD in the US and the SHC in Belgium, respectively. For RSVpreF (Abrysvo®), the overall certainty of evidence regarding its efficacy against RSV LRTI and medically attended LRTI was considered to be moderate by the NCIRD.[162] Comparisons between the vaccines are challenging. As noted by the JCVI in their advice, no head-to-head studies of the vaccines have been published while results of the respective clinical trials for each vaccine are not directly comparable, as they used different case definitions and end points.[102] Currently there is an absence of published observational evidence on the effectiveness of RSV vaccines for older adults in real-world settings. As such, the duration of protection provided by RSV vaccines for older adults is unclear, and is a matter for further consideration.

Both vaccines were considered to have acceptable safety profiles by the NCIRD, with evidence of serious adverse events considered to be of high certainty.[153, 162] However, the NCIRD noted that the certainty of evidence relating to inflammatory neurologic events could not be assessed for RSVPreF3 (Arexvy®), and was deemed to be of low certainty for RSVpreF (Abrysvo®).[153, 162] A small number of such events have been recorded for each vaccine in clinical trials to date (three events in 17,922 participants for RSVPreF3 (Arexvy®) and three in 20,255 participants for RSVpreF (Abrysvo®) with countries noting in their national recommendations that further safety data are needed based on post-marketing surveillance.[11, 135, 143, 147] The CDC and FDA in the US are monitoring post-licensure RSV vaccine safety, with monitoring for GBS specifically being undertaken through population-based active surveillance systems.[154]

Co-administration of RSV vaccines

Co-administration of RSV vaccines with seasonal influenza vaccines for older adults was thought to be acceptable in the recommendations of three EU/EEA countries (Belgium, Ireland and Norway). The Norwegian recommendation specifies that an RSV vaccine may only be co-administered with an influenza vaccine that does not contain an adjuvant. These countries' recommendations were primarily based on data relating to RSVPreF3 (Arexvy®) and, in Ireland, immunogenicity data from a phase 1/2 trial for RSVpreF (Abrysvo®).[152] Similar recommendations are also in place in the US.[147] The ACIP's recommendations note that co-administration may increase local or systemic reactogenicity, so separate injection sites or separate limbs should be selected for administration, and consideration should be given to the patient's risk profile, preferences, and feasibility of returning for a separate vaccine dose. As of 1 July 2024, co-administration of RSV vaccines with other vaccines frequently recommended for older adults (for example, COVID-19 vaccines) is not recommended in any EU/EEA country, in the UK, or in the US. Further safety data are required to enable recommendations to be made regarding co-administration of RSV vaccines in such contexts.

3.5.3 Conclusion

Overall, international practice with respect to recommendations for, and implementation of, immunisation of infants and older adults against RSV is a rapidly changing area. It is likely that countries will continue to develop new recommendations and update existing recommendations in light of further evidence, particularly national data on the epidemiology and burden of RSV disease, as well as RSV surveillance data from countries that have offered RSV immunisation programmes during the 2023-2024 RSV season. Published trial data for nirsevimab, the maternal vaccine and RSV vaccines for older adults that supported recommendations in the countries included in the review suggest that these agents

are safe and effective. Moreover, early evidence of real-world safety and effectiveness of nirsevimab from countries that implemented immunisation for infants in the 2023-2024 season are consistent with these trial data. Chapter 4 will describe and discuss the epidemiology and burden of RSV disease in Ireland. In Chapter 5, a costing analysis will be outlined to provide an indication of costs associated with an RSV immunisation programme in Ireland.

4 Epidemiology and Burden of Disease

Key points

- Respiratory syncytial virus (RSV) is a highly contagious respiratory illness. Although in many cases the symptoms are mild, complications can occur. Groups vulnerable to serious complications include infants, young children and older adults. Protective immunity from prior exposure to RSV is not life-long and therefore a large proportion of the population is susceptible to RSV infection each season. RSV has been a notifiable disease in Ireland since 2012.
- RSV incidence data were sourced from the Health Protection Surveillance Centre (HPSC) in Ireland for 2013 to 2023. Hospital utilisation data were sourced from the Hospital In-Patient Enquiry (HIPE) system for 2013 to 2022. For those aged 0 to 4 years, acute bronchiolitis data were also sourced from HIPE for the same period. Estimated averages exclude 2020 as these data are not considered representative due to the influence of the COVID-19 pandemic. Data typically were provided by calendar year rather than by RSV season.
- HPSC data indicate that for the period 2013 to 2023 the annual burden associated with RSV has varied, with the highest burden observed in 2022 (adults aged 65 years and older) and 2023 (children aged 0 to 4 years).
  - In children aged 0 to 4 years, annual rates have ranged from:
    - 335.1 to 1,699.6 per 100,000 for notified RSV cases
    - 34.0 to 785.0 per 100,000 for notified RSV emergency department (ED) visits
    - 190.3 to 790.1 per 100,000 RSV-related hospital admissions.
  - In children aged less than one year, annual rates have ranged from:
    - 1,368.6 to 4,910.4 per 100,000 for notified RSV cases
    - 142.2 to 2,190.5 per 100,000 for notified RSV ED visits
    - 783.0 to 2,456.9 per 100,000 RSV-related hospital admissions.
  - In adults aged 65 years and older, annual rates have ranged from:
    - 6.4 to 203.9 per 100,000 for notified RSV cases
    - 9.5 to 58.7 per 100,000 for notified RSV ED visits
    - 1.3 to 74.6 per 100,000 for RSV-related hospital admissions.
  - In adults aged 80 years and older, annual rates have ranged from:
    - 11.7 to 412.6 per 100,000 for notified RSV cases
    - 16.6 to 115.5 per 100,000 for notified RSV ED visits
    - 2.0 to 151.9 per 100,000 for RSV-related hospital admissions.

- The burden of RSV is substantially higher in infants aged less than one year compared with all other age bands examined as part of this assessment (those aged 1 to 4 and adults aged 65 years and older).
  - Among those aged 0 to 4 years, infants aged less than one year accounted for, on average, 67% (range: 57% to 83%) of notified cases, 64% (range: 55% to 85%) of RSV-related ED visits and 69% (range: 57% to 84%) of RSV-related hospital admissions.
  - HPSC data relating to notified RSV hospital admissions for those aged 0 to 2 years were provided for the 2022-2023 season.
    - Infants aged less than one year accounted for 69% (n=1,124) of notified hospital admissions, with 74% (n=834) of this burden in those aged less than six months (that is, 51% of all admissions in those aged 0 to 2 years occurred in those aged less than six months).
  - Among older adults, burden typically increased with age. Adults aged 80 years and older accounted for 46% (range: 35% to 48%) of notified cases, 43% (range: 40% to 46%) of RSV-related ED visits and 46% (range: 29% to 50%) of RSV-related hospital admissions.

- In Ireland, RSV outbreaks typically occur in the winter months with the highest numbers of infections usually reported in December and January every year. When assessed by calendar month, HPSC data for the period 2019 to 2023 indicated that for those aged:
  - 0 to 4 years, increased notifications generally occurred from September to the end of January with notifications peaking in November
  - 65 years and older, increased notifications generally occurred from October to the end of March with notifications peaking in December.

- HIPE data showed that there is a substantial burden associated with RSV in those aged between 0 and 4 years. In those with a primary diagnosis of RSV, on average, each year:
  - there were 1,341 (range: 790 to 2,259) discharges that did not include an intensive care unit (ICU) stay (infants aged less than one year accounted for 84% of these discharges). The mean hospital length of stay (LOS) was four days and the mean total bed days associated with these discharges was 4,874 days (range: 3,118 to 7,377) per annum.
  - there were 121 (range: 62 to 201) discharges that included an ICU stay (infants aged less than one year accounted for 90% of these discharges). The mean hospital LOS was thirteen days and the mean total bed days associated with these discharges was 1,482 days (range: 926 to 1,956) per annum.

  - hospital discharges in quarter four accounted for the greatest proportion of annual discharges, ranging from 71% in 2018 to 91% in 2021 (of those without an ICU stay), and from 61% in 2018 to 91% in 2021 (of those that included an ICU stay).
  - the average cost of bed days was approximately €10.4 million per annum (range: €6 million to €17.5 million) for discharges that did not include an ICU stay, and €4.1 million (range: €2.6 million to €5.1 million) for discharges that included an ICU stay.

- HIPE data indicate that in adults aged 65 years and older, the number of discharges is relatively low. From 2013 to 2022:
  - there were a total of 225 discharges and 2,154 bed days (of which 134 and 1,302 were recorded in 2022, respectively).
  - discharges that included an ICU stay were uncommon, with fewer than five discharges a year recorded in those aged 65 years and older in all but one of the years over this time period.
  - the mean annual cost associated with hospital discharges that did not include an ICU stay was €0.4 million, although these data were highly skewed (range: €0 to €1.3 million).

- HIPE data (2013 to 2022) indicate that annual RSV-related mortality rates were consistently low. In those with a primary diagnosis of RSV:
  - rates ranged from 0.0 to 0.9 per 100,000 in those aged 0 to 4 years.
  - the majority of annual mortality data were suppressed in those aged 65 years and older due to small count numbers (1 to 5), with no deaths reported in 2013. The highest rate was reported in 2022 (2.4 per 100,000; n=19).

- These data are likely an underestimate of the total burden of RSV, as not all RSV cases are laboratory confirmed and some discharges may not be coded. While there is an apparent trend of increasing incidence over time, this may reflect greater detection rather than a true increase in burden.
  - Testing practices have changed and there has been a three-fold increase in onsite laboratory multiplex RT-PCR testing capacity for respiratory viruses since COVID-19.
  - RSV is noted to be the most common cause of acute bronchiolitis in young children. When considering the combined burden associated with RSV and acute bronchiolitis cases (primary diagnosis) in children aged 0 to 4 years, HIPE data indicate that the proportion of hospital discharges coded as acute bronchiolitis has decreased from 67% in 2013 to 39% in 2022.

- There is currently no RSV immunisation programme implemented in Ireland for the general infant or older adult population. However, palivizumab is currently offered to children identified to be at high risk of severe disease from RSV infection during their first and second RSV seasons. From 2019 and 2023, the number of children aged 0 to 4 years who have accessed palivizumab in primary care has ranged from 627 in 2021 to 768 in 2019.
- Uptake of existing immunisation programmes offered to infants, pregnant women and older adults were assessed to inform potential uptake of RSV immunisation strategies in these populations:
  - Currently, the earliest immunisation of infants occurs at two months of age. HPSC data for the period 2018 to 2022 indicate that uptake of the primary immunisation schedule (all vaccines) in infants aged up to 12 months has ranged from 87.2% to 90.0%.
  - There are very limited nationally collected data relating to uptake of vaccines routinely offered to pregnant women (seasonal influenza, COVID-19, pertussis).
  - In adults aged 65 years and older:
    - Uptake of the seasonal influenza vaccination was 76.5% in the 2022-2023 flu season.
    - While uptake of the primary course and first booster of the COVID-19 vaccine was high (99.4% and 95.7%, respectively), uptake of the 2023-2024 autumn booster was 56.5%.
  - Reported barriers to uptake in these populations include perceived low risk of illness, lack of knowledge or information, and concerns in relation to the effectiveness and safety of the vaccine.
- There is currently a lack of data on the wider burden of RSV in Ireland and internationally. The limited international data available suggest that hospitalisation of a child negatively impacts parents' and or carers' health-related quality of life, job productivity and family health and functioning. In older adults, RSV has been reported to negatively impact the daily activities, productivity, social activities, relationships and employment of those infected.
- In summary, RSV places a significant burden on secondary healthcare services, with the highest burden seen in infants aged less than one year. RSV poses a particular challenge for paediatric healthcare services, as a high proportion of hospital discharges occur in quarter four each year. While testing capacity has increased, the identified data are likely an underestimate of the total burden, as not all RSV cases are laboratory confirmed and some discharges may not be coded.

4.1 Introduction

This chapter describes the epidemiology of respiratory syncytial virus (RSV) and the burden of disease in Ireland, EU/EEA countries and the UK among infants and older adults (that is, those aged 65 years and older).

RSV is a highly contagious respiratory illness. In many cases, the disease is mild, with symptoms such as a cough, fever and runny nose. However, RSV can also result in serious complications, particularly in infants, young children, older adults (that is, those aged 65 years and older), people with an underlying lung or heart condition, and people with a weakened immune system. The infectious period of RSV lasts from shortly before symptom onset, to about one week after symptom onset; however, infants and children may be contagious for up to four weeks.[14]

RSV is largely contracted via droplets and contact as people sneeze or cough. It can also survive on hard surfaces such as worktops and doorknobs for up to six hours. Protective immunity arising from prior exposure to RSV is not life-long and therefore a large proportion of the population is susceptible to infection each season, but disease severity tends to be reduced with repeated exposure.[5] In the Northern Hemisphere, RSV activity generally peaks during the winter months (mostly between December and January); however, peaks can occur earlier.[22]

4.2 Data sources

The focus of this HTA is on RSV, which can be acquired at any time of year, but is most common in winter months. Surveillance of RSV refers to the collection, aggregation and analysis of RSV activity information for a defined population for a specified period of time. RSV surveillance involves collection of both clinical and virological data. Clinical surveillance monitors the impact of the illness on the health service and the community, while the purpose of virological surveillance is to identify when RSV is circulating and the current strain.[163]

RSV has been a notifiable disease in Ireland since 2012 under the Infectious Disease Regulations and it is mandatory for clinicians and laboratories to notify RSV cases to the Medical Officer of Health. Notifications are reported using the Irish Computerised Infectious Disease Reporting system (CIDR). Cases are classified as possible, probable or confirmed, with the latter dependent on the person meeting stated clinical and laboratory criteria. Surveillance of all confirmed RSV notifications, including hospitalisations and outbreaks, are reported through the CIDR notification system.

The HPSC also work in collaboration with the Irish College of General Practitioners (ICGP), the National Virus Reference Laboratory (NVRL), and the Departments of

Public Health. The Irish Sentinel GP network was established in 2000 and as of October 2022 comprised 61 general practices covering approximately 6.9% of the national population. Sentinel practices are located in all HSE regions and are selected based on the population of each region. Expansion of the sentinel GP network began during the 2022-2023 season gradually increasing the number of practices from 60 to 100 sentinel GP sites from October 2022 to February 2024. The system now covers approximately 18% of the population of Ireland and has improved the geographical representation of the Irish sentinel GP network. Sentinel GPs report electronically, on a weekly basis, the number of patients who consult with Acute Respiratory Infection (ARI) and influenza-like illness (ILI). Sentinel GPs systematically sample the first five patients presenting to their practice each week with symptoms of ARI and send combined nose and throat swabs from these patients to the NVRL for respiratory virus testing.

The NVRL routinely tests sentinel GP ARI and non-sentinel respiratory specimens for influenza, RSV, SARS-CoV-2 and a panel of other respiratory viruses. Non-sentinel respiratory specimens include specimens referred to the NVRL for testing from a variety of sources including hospitals, GPs (not part of sentinel GP network) and nursing homes for clinical or public health reasons and may include more than one specimen from each case.

For this HTA, RSV surveillance data for those aged 0 to 4 years and those aged 65 years and older were gathered from the sentinel GP network, non-sentinel specimens, CIDR and the NVRL for the period 2013 to 2023; these data were provided to HIQA by the HPSC. Data relating to the incidence of notified RSV cases were reported by month; data relating to laboratory-confirmed emergency department (ED) visits and hospital admissions were reported by calendar year. Data were extracted from CIDR and the HPSC sentinel surveillance system on 6 February 2024. Recommendations from the National Immunisation Advisory Committee (NIAC) in Ireland regarding immunisation of children against RSV, broadly relate to children aged less than two years, depending on the presence of risk factors. For this assessment, data were gathered for those aged 0 to 4 years to provide context for the proportion of paediatric burden that specifically occurs in infants aged less than one year and less than two years. The aim was to highlight the extent to which the burden in the paediatric population may be alleviated by an effective RSV immunisation strategy.

Rates were calculated using Central Statistics Office (CSO) census denominator data for the total and associated age-stratified population of Ireland. Census data from 2011[(164)] were used for the 2013 RSV analyses. Census data from 2016[(165)] were used for the 2014 to 2019 RSV analyses. Census data from 2022[(166)] were used for the 2020 to 2023 RSV analyses.

Data from the Hospital In-Patient Enquiry (HIPE) system were also gathered to understand the nature of RSV hospitalisations (for example, complications of the disease and length of stay). These data were provided quarterly and by calendar year (not by RSV season). Data from the HIPE system in Ireland were used to examine hospital discharges with and without an intensive care unit (ICU) stay for those aged 0 to 4 years with a primary or secondary diagnosis of RSV (with ICD-10 codes B97.4, J12.1, J20.5, J21.0). RSV commonly presents as acute bronchiolitis in children and is noted to be the most common cause of acute bronchiolitis in young children. Given the potential that the burden of RSV is underestimated due to a lack of testing, for context, hospital discharge data were also obtained for those with a primary diagnosis of acute bronchiolitis (with ICD-10 codes J21.8 and J21.9). HIPE data were also used to examine hospital discharges with and without an intensive care unit (ICU) stay for adults aged 65 years or older with a primary or secondary diagnosis of RSV (with ICD-10 codes B97.4, J12.1, J20.5, J21.0). Acute bronchiolitis is rare in adults and may be caused by a range of factors, therefore this diagnosis was not considered relevant for those aged 65 years and older. A HIPE discharge record is created when a patient is discharged from, or dies in, hospital. This record contains information for a discrete episode of care. An episode of care begins at admission to hospital, as a day or inpatient, and ends at discharge from (or death in) that hospital.[167] HIPE data are used to create Diagnosis Related Groups to inform Activity Based Funding,[168] which is a funding model for hospital care for inpatient and day-case services.[169] Using this model, a specified price is paid to each hospital for each weighted unit of inpatient and day-case work undertaken. Data provided by HIPE for this assessment also included the total cost of discharges, reported separately for those with and without an ICU stay, for all included diagnoses.

4.3 Incidence of RSV

4.3.1 Incidence of RSV in Ireland (those aged 0 to 4 years)

Notified RSV incidence per 100,000 for those aged 0 to 4 years are reported in Table 4.1. For 2023, data indicate notified case rates of 4,910.4 per 100,000 (n=2,838) in infants aged less than one year, 1,331.0 per 100,000 (n=1,539) in those aged one to two years, and 527.9 per 100,000 (n=644) in those aged three to four years. In those aged 0 to 4 years, the notified case rate reported for 2023 (1,699.6 per 100,000) was the highest observed across all 11 years of data examined as part of this HTA. Infants aged less than one year accounted for the largest proportion of annual notified RSV cases in those aged 0 to 4 years (mean per annum: 67%, range: 57% to 83%). This proportion has declined from 83% in 2013 to 57% in 2023, with the remaining age bands accounting for increasing proportions of notified RSV cases over this time.

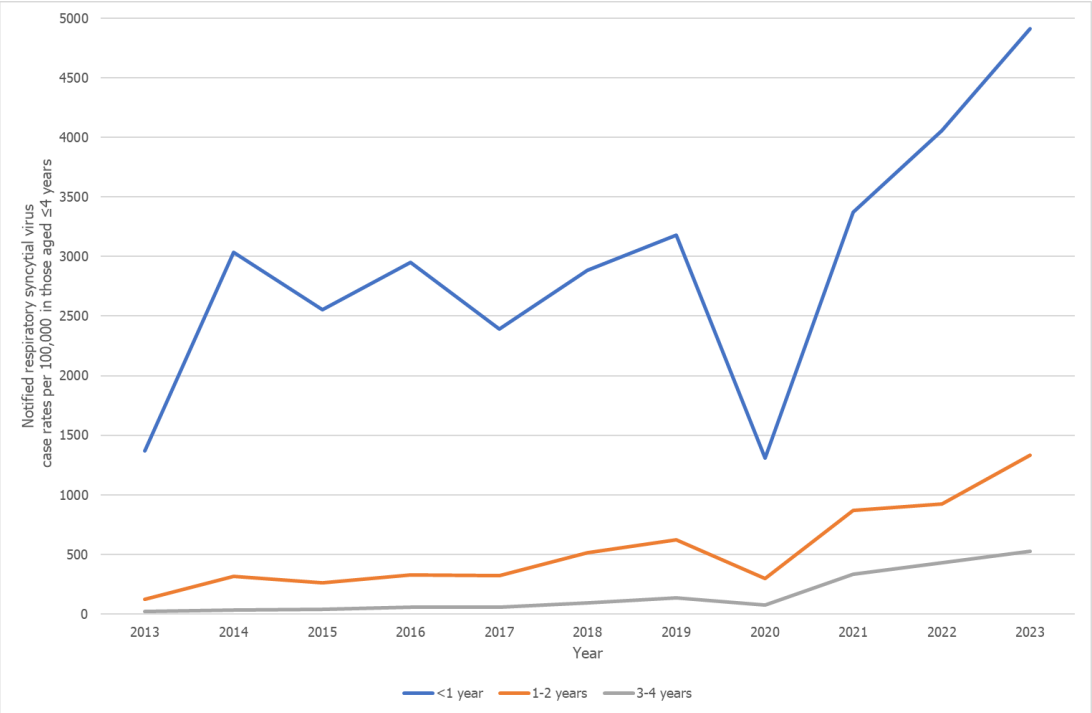
Table 4.1 Notified RSV cases for those aged 0 to 4 years in Ireland, reported by age band

Year	0-4 years		<1 year		1-2 years		3-4 years	
	n	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000
2013	1,194	335.1	991 (83)	1,368.6	177 (15)	121.9	26 (2)	18.7
2014	2,349	708.6	1,889 (80)	3,034.2	410 (17)	314.5	50 (2)	36.0
2015	1,982	597.9	1,589 (80)	2,552.3	339 (17)	260.1	54 (3)	38.9
2016	2,349	708.6	1,837 (78)	2,950.7	429 (18)	329.1	83 (4)	59.8
2017	1,987	599.4	1,487 (75)	2,388.5	418 (21)	320.7	82 (4)	59.0
2018	2,594	782.5	1,795 (69)	2,883.2	667 (26)	511.7	132 (5)	95.0
2019	2,979	898.6	1,981 (66)	3,182.0	810 (27)	621.4	188 (6)	135.3
2020	1,188	402.1	756 (64)	1,308.0	342 (29)	295.8	90 (8)	73.8
2021	3,360	1,137.4	1,948 (58)	3,370.5	1,004 (30)	868.3	408 (12)	334.5
2022	3,941	1,334.1	2,346 (60)	4,059.1	1,070 (27)	925.4	525 (13)	430.4
2023	5,021	1,699.6	2,838 (57)	4,910.4	1,539 (31)	1,331.0	644 (13)	527.9
Mean per annum*	**2,776**		**1,870 (67)**		**686 (25)**		**219 (8)**	

*Mean per annum excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic.
Source: Health Protection Surveillance Centre.

In general, the incidence of notified RSV cases has increased over time for those aged 0 to 4 years. However, there has been a substantial increase in testing capacity since 2016, and changes in testing patterns since the COVID-19 pandemic (such as increased used of multiplex reverse transcriptase polymerase chain reaction (RT-PCR) assays), both of which could also have an impact on the incidence reported. Caution is therefore required in inferring temporal trends based on the data presented. The notified RSV case rate per 100,000 for those aged 0 to 4 years are presented by age band and year in Figure 4.1. Rates were consistently highest in infants aged less than one year and decreased with increasing age within this cohort.

Figure 4.1 Notified RSV case rate per 100,000 in those aged 0 to 4 years in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

4.3.2 Incidence of RSV in Ireland (older adults)

Notified RSV incidence per 100,000 for adults aged 65 years and older are reported in Table 4.2. For 2023, data indicate notified case rates of 99.1 per 100,000 (n=236) in those aged 65 to 69 years, 124.7 per 100,000 (n=253) in those aged 70 to 74 years, 173.7 per 100,000 (n=268) in those aged 75 to 79 years, 274.4 per 100,000 (n=265) in those aged 80 to 84 years, and 464.2 per 100,000 (n=392) in those aged 85 years and older. The incidence of RSV increased with each increased age band. In those aged 65 years and older, the notified case rate reported for 2022 (203.9 per 100,000) was the highest observed across all 11 years of data examined as part of this HTA. In general, adults aged 80 years and older accounted for 46% (range: 35% to 48%) of notified RSV cases in adults aged 65 years and older. In those aged 80 years and older, the notified case rate ranged from 11.7 to 412.6 per 100,000, in 2013 and 2022, respectively.

Table 4.2 Notified RSV cases for adults aged 65 years and older in Ireland, reported by age band

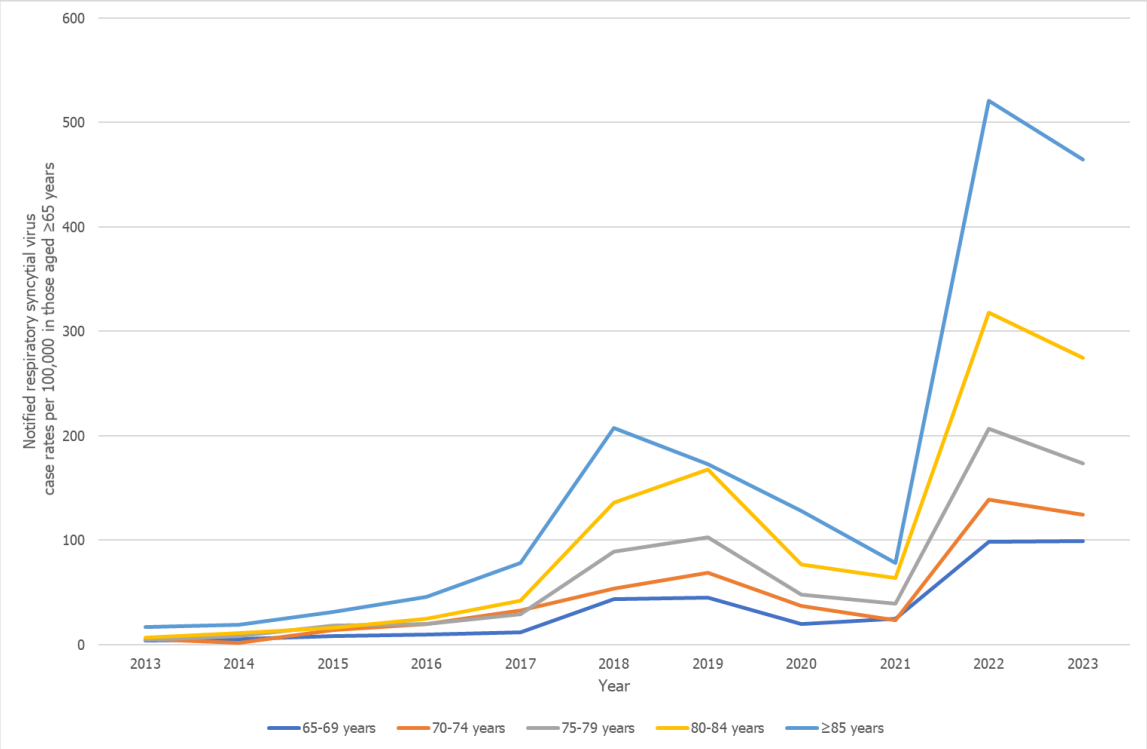
Year	≥65 years		65-69 years		70-74 years		75-79 years		80-84 years		≥85 years	
	N	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000
2013	34	6.4	7 (21)	4.0	7 (21)	5.3	5 (15)	4.9	5 (15)	7.1	10 (29)	17.1
2014	46	7.2	11 (24)	5.2	3 (7)	1.8	10 (22)	8.7	9 (20)	11.1	13 (28)	19.2
2015	96	15.1	18 (19)	8.5	23 (24)	14.2	21 (22)	18.2	13 (14)	16.0	21 (22)	31.1
2016	126	19.8	20 (16)	9.5	32 (25)	19.7	23 (18)	19.9	20 (16)	24.7	31 (25)	45.9
2017	199	31.2	25 (13)	11.8	53 (27)	32.7	34 (17)	29.4	34 (17)	42.0	53 (27)	78.5
2018	533	83.6	93 (17)	44.0	87 (16)	53.6	103 (19)	89.2	110 (21)	135.7	140 (26)	207.2
2019	580	91.0	96 (17)	45.4	112 (19)	69.0	119 (21)	103.1	136 (23)	167.8	117 (20)	173.2
2020	379	48.8	48 (13)	20.2	75 (20)	37.0	74 (20)	48.0	74 (20)	76.6	108 (28)	127.9
2021	296	38.1	59 (20)	24.8	48 (16)	23.7	61 (21)	39.5	62 (21)	64.2	66 (22)	78.2
2022	1,583	203.9	235 (15)	98.7	282 (18)	139.0	319 (20)	206.8	307 (19)	317.9	440 (28)	521.1
2023	1,414	182.1	236 (17)	99.1	253 (18)	124.7	268 (19)	173.7	265 (19)	274.4	392 (28)	464.2
Mean per annum*	**491**		**80 (16)**		**90 (18)**		**96 (20)**		**96 (20)**		**128 (26)**	

*Mean per annum excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic.

Source: Health Protection Surveillance Centre.

In general, the incidence of notified RSV cases has increased over time in adults aged 65 years and older. However, as already highlighted, there have been changes in testing capacity and patterns, particularly since the COVID-19 pandemic, both of which could also have an impact on the incidence reported. Caution is therefore required in inferring temporal trends based on the data presented. The notified RSV case rate per 100,000 for adults aged 65 years and older are presented by age band and year in Figure 4.3. Rates typically increased with increasing age and were consistently highest in those aged 85 years and older.

Figure 4.3 Notified RSV case rate per 100,000 for adults aged 65 years and older in Ireland, reported by age band and year

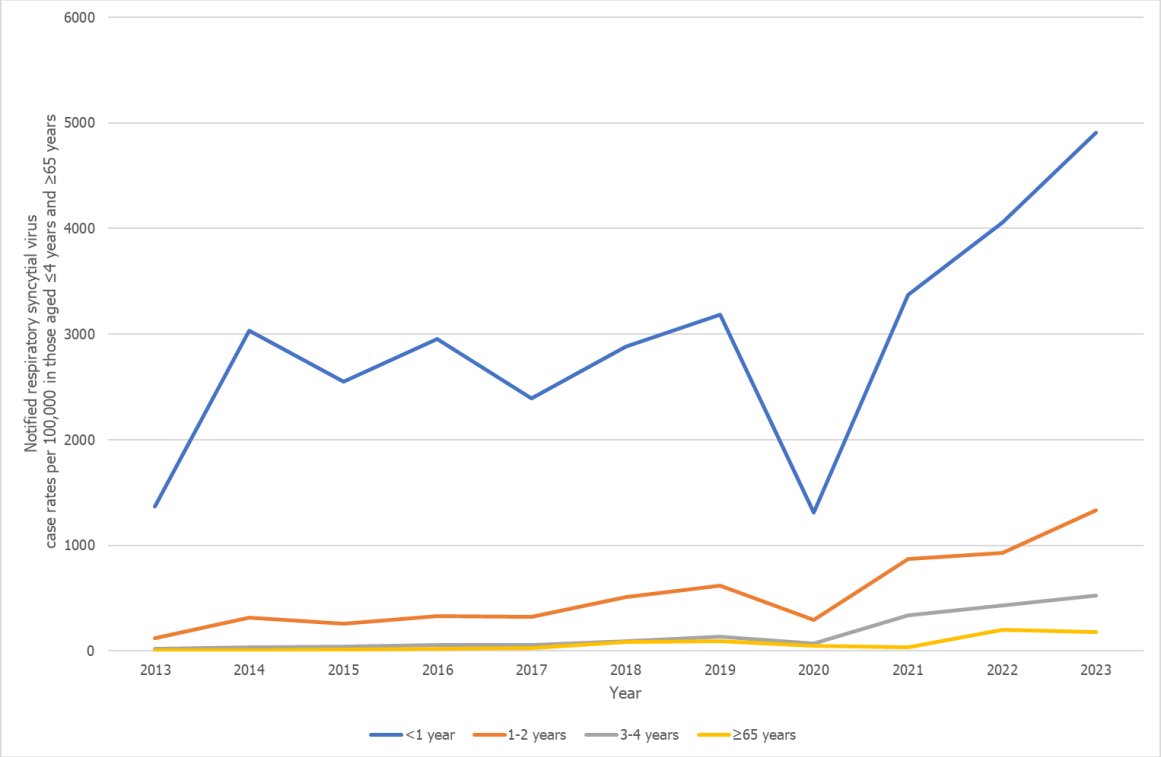


Source: Health Protection Surveillance Centre.

4.3.3 Comparison of RSV incidence in those age 0 to 4 years and in older adults

The notified RSV case rate per 100,000 for those aged 0 to 4 years and adults aged 65 years and older are presented by age band and year in Figure 4.5. As depicted, the burden of RSV is considerably higher in infants aged less than one year compared to all other age bands.

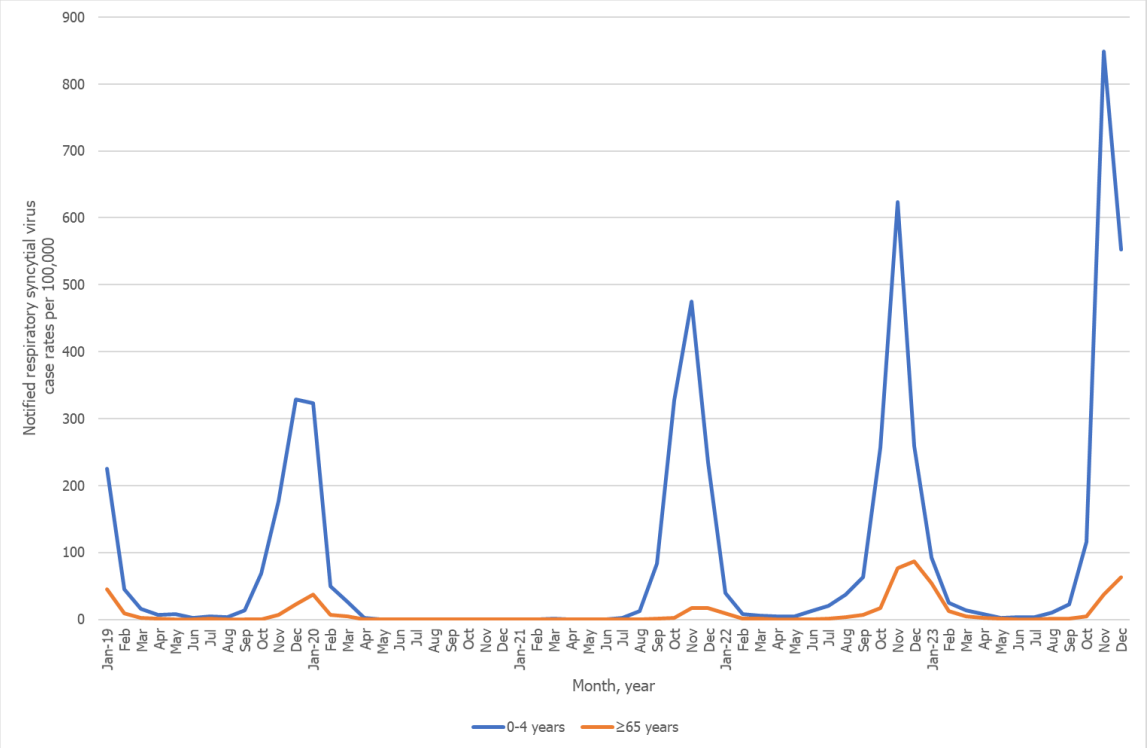
Figure 4.5 Notified RSV case rate per 100,000 for those aged 0 to 4 years and adults aged 65 years and older in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

Figure 4.6 provides an overview of the notified RSV case rate per 100,000 for those aged 0 to 4 years and adults aged 65 years and older, reported by month (for years 2019 to 2023). As expected, seasonal outbreaks occurred each year. During these years, rates typically began to peak a little earlier (one to two months earlier) in those aged 0 to 4 years with increased notifications generally noted from September through to the end of January in this cohort compared with October to the end of March in those aged 65 years and older. For this period, notifications peaked in November for those aged 0 to 4 years compared with December in older adults.

Figure 4.6 Notified RSV case rate per 100,000 in those aged 0 to 4 years and adults aged 65 years and older in Ireland, reported by month (for years 2019 to 2023)



Source: Health Protection Surveillance Centre.

Access to testing for RSV is thought to differ between settings, with the perception that incidence in primary care is underestimated due to limited testing. HPSC data in relation to specimens received from primary care were reviewed to assess the volume of testing in primary care for those aged 0 to 4 years and in those aged 65 years and older.

From 2013 to 2023, and excluding the year 2020, the annual number of specimens from sentinel practices tested for RSV has generally increased over time. In children aged 0 to 4 years, on average 177 specimens (range: 10 in 2015 to 945 in 2021) were tested per annum, compared to an average of 277 specimens (range: 49 in 2014 to 925 in 2021) in those aged 65 years and older. Of note, the sizes of these populations differ substantially, Census 2022 data report that there were 295,415 children aged 0 to 4 years and 776,315 adults aged 65 years and older.[170] The percentage positivity from sentinel specimens was low, with an average of 10% positivity per annum (range: 0% in 2015 to 21% in 2023) in those aged 0 to 4 years and 4% per annum (range: 0% in 2013 to 8% in 2019) in those aged 65 years and older. In those aged 0 to 4 years, on average, almost 90% of specimens related to those aged between one and four years, with the highest percentage positivity in those aged one to two years (13%). For those aged 65 years and older, when

stratified by five-year age band, the highest number of specimens tested was in those aged 65 to 69 years (33%), with little difference seen in the average percentage positivity (range 4% to 6%) across age bands.

Although not considered to be a nationally representative sample, from 2013 to 2023, the number of specimens from non-sentinel GP practices tested per calendar year has generally increased over time. Excluding data from 2020 from the calculations, in children aged 0 to 4 years, on average 3,085 specimens (range: 1,242 in 2013 to 6,139 in 2019) were tested per annum, compared to an average of 1,710 specimens (range: 640 in 2013 to 3,343 in 2018) in those aged 65 years and older. The percentage positivity was higher than that observed from sentinel specimens, with an average positivity of 30% per annum (range: 7% in 2023 to 56% in 2014) in those aged 0 to 4 years. In those aged 65 years and older, the percentage positivity was only slightly higher than that observed from sentinel specimens; the average percentage positivity was 7% per annum (range: 2% in 2021 to 12% in 2016) in those aged 65 years and older. For those aged 0 to 4 years, on average, the highest number of specimens tested related to those aged less than one year (56%) with the highest average percentage positivity (35%) noted in this group. When stratified by five-year age band, the highest number of specimens tested in older adults was in those aged 85 years and older (26%) with average percentage positivity ranging from 6% to 9%.

4.3.4 Incidence of RSV in EU/EEA countries and the UK

Since 2014, influenza surveillance in Europe has been jointly coordinated by the World Health Organization Regional Office for Europe (WHO/Europe) and the European Centre for Disease Prevention and Control (ECDC). Surveillance data from the 53 countries of the WHO/Europe Region (which includes the 30 EU/EEA countries) are submitted to a joint ECDC-WHO/Europe database, the European Surveillance System (TESSy).[171] While this surveillance focuses on the mandatory reporting of influenza data, historically, countries may also submit national RSV surveillance data, where available. However, RSV is currently not a mandatory, reportable disease at EU level; therefore, RSV surveillance data submitted to TESSy is based on voluntary reporting, and so is incomplete. As of 2022, RSV was a notifiable disease in only 12 European countries.[171] This has resulted in a number of limitations to the RSV data which the ECDC collects. Limitations include heterogeneity among the surveillance systems providing RSV data to the ECDC, in terms of sampling strategy, population, and setting (primary or secondary care).[171]

In July 2022, the ECDC released guidance related to respiratory virus surveillance in Europe.[172] This guidance encouraged EU/EEA member states to strengthen population-based surveillance in primary and secondary care,[173] and outlined

objectives in relation to the integrated surveillance of influenza, SARS-CoV-2 and other respiratory viruses, including RSV.[172] Objectives included testing those who presented with respiratory symptoms (at sentinel sites) for a large range of respiratory viruses, including RSV, and reporting this data at European level. This surveillance data is currently submitted to TESSy, and since October 2023, is hosted in the European Respiratory Virus Surveillance Summary (ERVISS).[174] These data are currently presented weekly by the ECDC within a respiratory virus update.[175] However, data in ERVISS are not disaggregated into age cohorts relevant for this HTA — that is, those aged 0 to 4 years and adults aged 65 years or older.

The PROMISE initiative (Preparing for RSV Immunisation and Surveillance in Europe), funded by the Innovative Medicines Initiative, also publishes a bi-weekly, WHO/Euro-ECDC integrated, RSV surveillance bulletin.[176] This bulletin provides an overview of SARS-CoV-2, influenza and RSV surveillance data, provided voluntarily from National Public Health Institutes, in selected EU/EEA countries.[177] However, as with the weekly ECDC update, the PROMISE RSV bulletin does not provide disaggregated data (specifically, RSV incidence) in those aged 0 to 4 years, and adults aged 65 years or older.

A 2024 systematic analysis of Global Burden of Disease (GBD) Study 2021 data outlined that internationally, lower respiratory infection (LRI) (defined as pneumonia or bronchiolitis cases) episodes attributable to RSV increased from 10.6 million (95% uncertainty interval (UI): 9.6 million to 11.5 million) in 1990, to 12.5 million (95% UI: 11.5 million to 13.7 million) in 2019, and decreased during the COVID-19 pandemic to 4.6 million (95% UI: 3.3 million to 6.0 million) in 2021 (63.2% reduction).[178] In the 2020-2021 winter season, European RSV activity levels were identified as extremely low.[21] A 2021 analysis of ECDC RSV surveillance-atlas data outlined that, of the 17 European countries for which data were available, only France and Iceland experienced RSV epidemics during the winter of 2020-2021.[21]

A 2023 analysis of RSV surveillance data submitted to TESSy supported this finding, with 195 RSV detections, from a total of 21,803 sentinel surveillance specimens tested, reported during the 2020-2021 winter season (overall positivity of 1%).[179] Following this period of low RSV activity, high out-of-season RSV circulation was reported in the summer of 2021, with three European countries (Germany , Netherlands and Slovenia) experiencing RSV epidemics. This was then followed by an earlier start of the RSV season in a number of European countries in 2021-2022 (including Denmark, Germany, Ireland and Slovenia).[179] It was suggested that both the increased circulation of RSV in the summer of 2021, and the earlier start of the RSV season in 2021-2022, may have been due to the low RSV circulation observed in the 2020-2021 winter season.[179]

There are currently limited longitudinal RSV surveillance data publically available, which includes the post-pandemic period. However, while still within the COVID-19 pandemic period (as defined by the WHO),[180] the 2022-2023 winter season was the first winter season since the beginning of the pandemic in which there were no significant non-pharmaceutical public health control measures in place internationally. A rapid risk assessment published by the ECDC in December 2022 (covering weeks 40/2022 to 47/2022) outlined that 23 EU/EEA countries had reported 25,838 RSV detections to TESSy from 244,325 specimens tested (pooled test positivity of 11%).[171] The ECDC also reported that the RSV season had started five weeks earlier than in pre-pandemic seasons (2017-2018 and 2019-2020),[171] and as of week 47/2022, 16 EU/EEA countries had reported RSV positivity rates of above 3%, for three or more consecutive weeks, on their surveillance systems.[181] In the UK, 2022-2023 winter RSV activity was reported by the UK Health Security Agency to be similar to previous seasons,[182] while Denmark reported an RSV epidemic 2.5 times higher than in pre-pandemic seasons.[183]

Children (aged 0 to 4 years)

International estimates of RSV incidence in those aged 0 to 4 years, while substantial, vary greatly, often dependent on methodologies used or dataset availability and composition. A 2022 global analysis by RESCEU (REspiratory Syncytial virus Consortium in EUrope) investigated the number of physician-confirmed diagnosis of acute lower respiratory infections (ALRI) with laboratory-confirmed RSV, and estimated that in 2019 there were 33.0 million RSV-associated ALRI cases (uncertainty range: 25.4 million to 44.6 million) in children younger than five years.[53] However, a 2024 systematic analysis of Global Burden of Disease Study (GBD) estimated (using multiple data sources including ICD-10 codes and microbial laboratory data) that in 2019 there were 7.4 million cases of LRI attributable to the RSV pathogen (95% UI: 6.5 million to 8.4 million) in children aged less than five years.[178]

During the pandemic, RSV activity in those aged 0 to 4 years followed similar trends to that of the general population. In the UK, RSV activity is monitored through a variety of primary and secondary care schemes. A 2023 retrospective, observational study of English national surveillance data from 2014 to 2022 outlined a total of 47 reported RSV cases in those aged less than five years in the 2020-2021 winter season.[184] This represented an estimated 99.5% (95% Prediction Interval (PI): -100.0 to -99.1) fewer RSV cases than predicted via regression modelling (n=10,327 [95% PI: 10,276 to 10,378]). In the 2021 summer season, an atypical peak in reported RSV cases (n=12,150) was then observed. This represented an estimated 1,258.3% (95% PI: 1,345.8 to 1,178.3) more RSV cases than predicted (n=895 [95% PI: 832 to 955]). In the 2021-2022 winter season, the number of reported

RSV cases (n=8,097) was similar to pre-pandemic seasons (average of 8,697 cases reported across 2015-2016 to 2019-2020); however, this number was an estimated 26.9% (95% PI: -27.0 to -26.8) less than predicted (n=11,078 [95% PI: 11,029 to 11,127]).[184] Similar RSV activity trends during the pandemic were observed in infants and young children in Denmark,[185] Germany[186] and Portugal.[187]

Germany also reported increased RSV activity in infants and young children in the 2022-2023 winter season.[186] An analysis was undertaken of RSV activity in those aged less than five years, recorded in national primary and secondary care sentinel surveillance systems, from 2011 to 2023. Laboratory-confirmed cases of RSV indicated that the winter 2022-2023 RSV season started earlier than pre-pandemic seasons.[186] Additionally, in primary care, the proportion of RSV diagnoses among acute respiratory infection cases (both defined via ICD-code diagnoses) was significantly higher in the 2023-2023 season (1.4% [95% Confidence Interval (CI): 1.3 to 1.4], 810 of 59,968, p<0.001), compared with pre-pandemic seasons (2011-2012 to 2019-2020: 0.5% [95% CI: 0.5 to 0.6], 988 of 188,173).[186] There is currently limited international evidence available regarding RSV incidence in those aged 0 to 4 years in the post-pandemic period.

Older adults (aged 65 years and older)

A 2020 systematic review and meta-analysis, including 36 studies and eight unpublished datasets, investigated the global burden of RSV-Acute Respiratory Infection (ARI) in adults aged 65 years and older.[188] The annualised incidence rate of RSV-ARI in adults aged 65 years and older in industrialised countries was estimated to be 6.7 cases (95% CI: 1.4 to 31.5) per 1,000 persons, per year.[188] This estimate was based upon laboratory-confirmed RSV-ARI incidence data provided in six studies, with industrialised countries defined as per the United Nations Children's Fund's classification 2015.[189] This incidence rate, when applied to the relevant regional populations (that is, in adults aged 65 years or older in industrialised countries), resulted in an estimation of 1.5 million episodes (95% CI: 0.3 million to 6.9 million) of RSV-ARI in this population in 2015. Within the systematic analysis of GBD 2021 data, RSV incidence estimates were not disaggregated by age band for adults aged 65 years and older. However, data were provided for adults aged 70 years and older, with RSV cases reported to have increased from 387,000 (95% UI: 341,000 to 442,000) in 1990, to 1.4 million (95% UI: 1.3 million to 1.6 million) in 2019, representing a 266.4% increase.[178]

During the COVID-19 pandemic, RSV activity in older adults followed a similar trend to that of infants, in which RSV levels were substantially reduced between April 2020 and May 2021. However, an analysis of RSV infections in the US between 2017 and 2022 outlined that while an atypical surge in RSV activity was observed in infants

less than five years in the late summer and autumn of 2021, this substantial surge was not observed in older adults (aged 65 years and older).[190] This was despite a 48% increase in RSV testing in older adults at that time. While COVID-19 public health measures had lessened during the late summer and autumn of 2021 in the US, it is possible older adults continued to exhibit behavioural change such as avoiding crowds, wearing masks and limiting visits to younger children, resulting in this reduced RSV transmission.[190]

It should be noted that a 2023 rapid literature review investigating the limitations of RSV epidemiological studies in older adults outlined that current studies are likely to underestimate the incidence of RSV infection in older adults.[191] Study limitations the authors suggested may impact RSV incidence estimation included a lack of routine testing for RSV in clinical practice; the use of case definitions and sampling periods not tailored specifically to RSV; studying a single season (with the potential for bias due to seasonal variability); and relying solely on PCR testing of upper respiratory tract samples compared with dual site sampling or addition of serology to detect RSV.[191]

4.4 Burden of disease

4.4.2 Complications and hospitalisations (those aged 0 to 4 years)

RSV-related emergency department visits

Notified RSV emergency department (ED) visit rates per 100,000 for those aged 0 to 4 years are reported in Table 4.3. For 2023, data indicate notified ED visit rates of 2,190.5 per 100,000 (n=1,266) in infants aged less than one year, 659.0 per 100,000 (n=762) in those aged one to two years, and 238.5 per 100,000 (n=291) in those aged three to four years. In those aged 0 to 4 years, the notified ED visit rate reported for 2023 (785.0 per 100,000) was the highest observed across all 11 years of data examined in the HTA. Infants aged less than one year accounted for the largest proportion of annual ED visits in those aged 0 to 4 years (mean per annum: 64%, range: 55% to 85%). This proportion has declined from 85% in 2013 to 55% in 2023, with the remaining age bands accounting for greater proportions of ED visits over time.

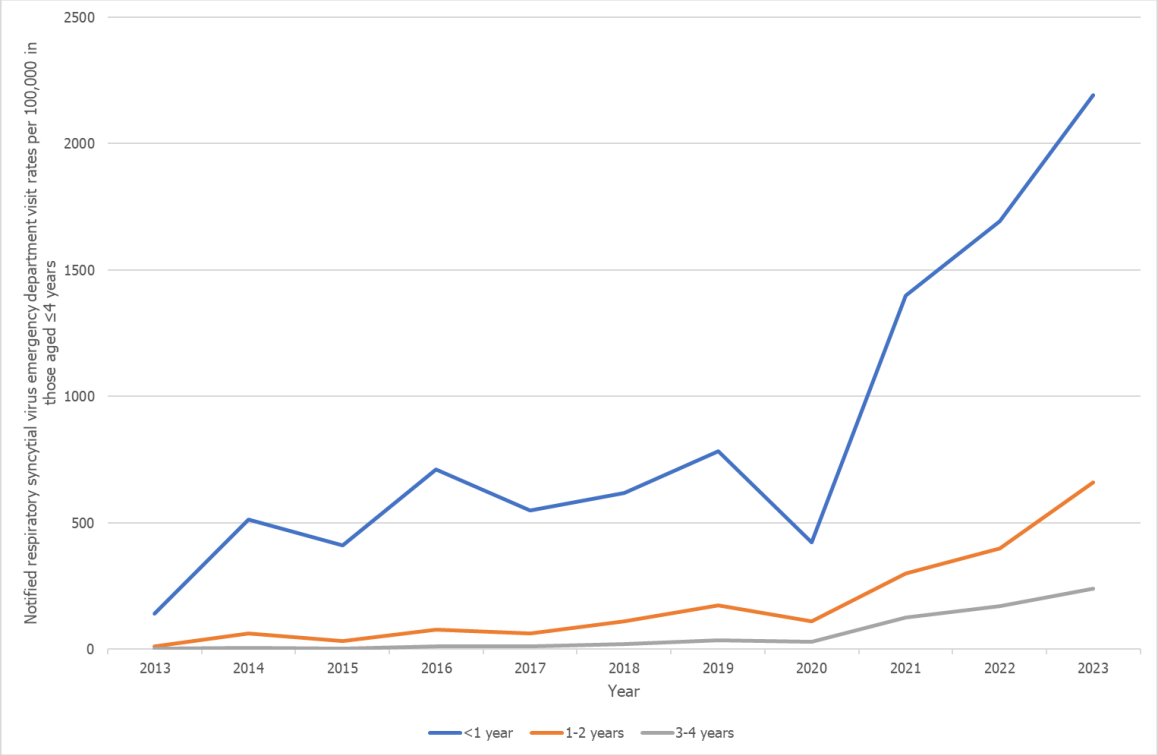
Table 4.3 Notified RSV emergency department visits in those aged 0 to 4 years in Ireland, reported by age band

Year	0-4 years		<1 year		1-2 years		3-4 years	
	n	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000
2013	121	34.0	103 (85)	142.2	16 (13)	11.0	2 (2)	1.4
2014	410	123.7	319 (78)	512.4	82 (20)	62.9	9 (2)	6.5
2015	304	91.7	256 (84)	411.2	43 (14)	33.0	5 (2)	3.6
2016	562	169.5	443 (79)	711.6	102 (18)	78.3	17 (3)	12.2
2017	439	132.4	342 (78)	549.3	82 (19)	62.9	15 (3)	10.8
2018	555	167.4	385 (69)	618.4	143 (26)	109.7	27 (5)	19.4
2019	766	231.1	487 (64)	782.2	228 (30)	174.9	51 (7)	36.7
2020	408	138.1	244 (60)	422.2	128 (31)	110.7	36 (9)	29.5
2021	1,309	443.1	808 (62)	1,398.0	347 (27)	300.1	154 (12)	126.2
2022	1,647	557.5	979 (59)	1,693.9	460 (28)	397.8	208 (13)	170.5
2023	2,319	785.0	1,266 (55)	2,190.5	762 (33)	659.0	291 (13)	238.5
Mean per annum*	**843**		**539 (64)**		**227 (27)**		**78 (9)**	

*Mean per annum excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic.
Source: Health Protection Surveillance Centre.

The notified RSV ED visit rates per 100,000 for those aged 0 to 4 years are presented by age band and year in Figure 4.7. Rates were consistently highest in infants aged less than one year. In general, the RSV ED visit rates have increased over time; however, as noted in section 4.3.1, this may relate to improved ascertainment due to changes in RSV testing patterns rather than a true increase in burden.

Figure 4.7 Notified RSV emergency department visit rates per 100,000 for those aged 0 to 4 years in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

RSV-related hospital admissions

Notified RSV hospital admission rates per 100,000 for those aged 0 to 4 years are reported in Table 4.4. For 2023, data indicate notified hospital admission rates of 2,456.9 per 100,000 (n=1,420) in infants aged less than one year, 562.1 per 100,000 (n=650) in those aged one to two years, and 216.4 per 100,000 (n=264) in those aged three to four years. In those aged 0 to 4 years, the notified hospital admission rate reported for 2023 (790.1 per 100,000) was the highest observed across all 11 years examined in this HTA. Infants aged less than one year accounted for the largest proportion of annual RSV hospital admissions in those aged 0 to 4 (mean per annum: 69%, range: 57% to 84%). This proportion has declined from 84% in 2013 to 61% in 2023, with the remaining age bands accounting for higher proportions of notified RSV hospital admissions over time.

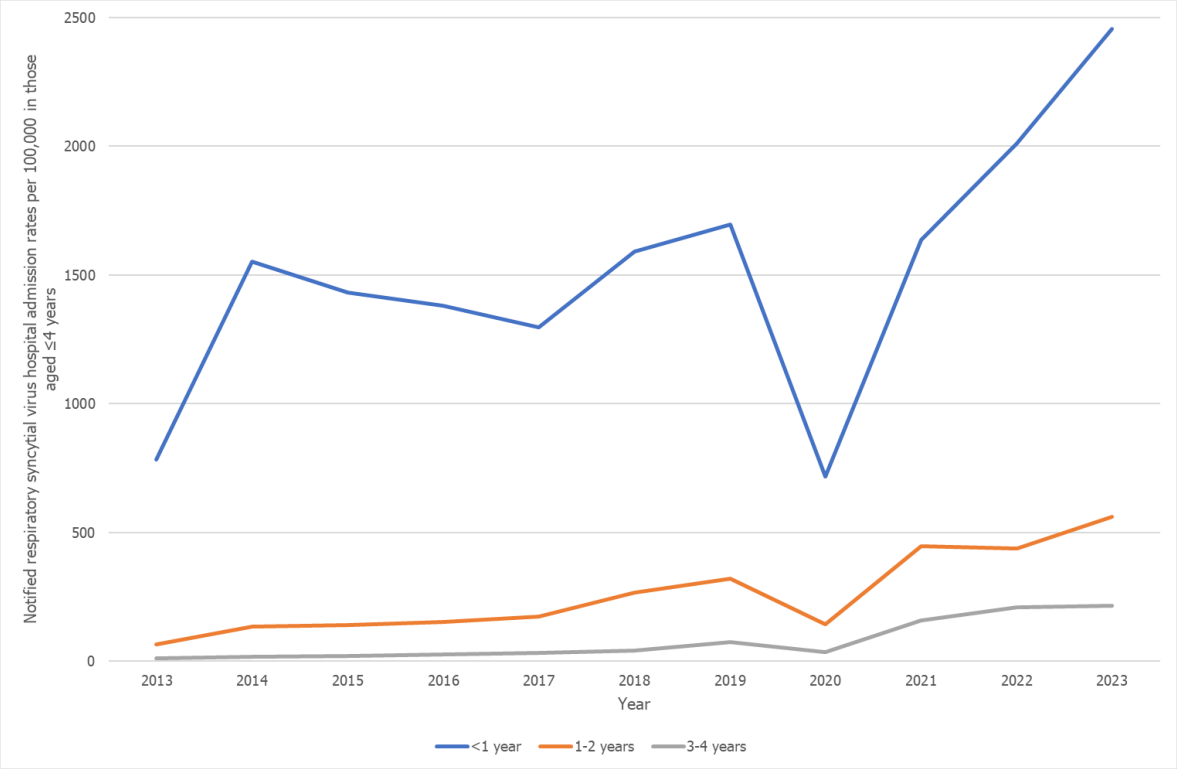
Table 4.4 Notified RSV hospital admissions for those aged 0 to 4 years in Ireland, reported by age band

Year	0-4 years		<1 year		1-2 years		3-4 years	
	n	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000
2013	678	190.3	567 (84)	783.0	96 (14)	66.1	15 (2)	10.8
2014	1,164	351.1	966 (83)	1,551.6	175 (15)	134.3	23 (2)	16.6
2015	1,103	332.7	892 (81)	1,432.8	184 (17)	141.2	27 (2)	19.4
2016	1,100	331.8	860 (78)	1,381.4	201 (18)	154.2	39 (4)	28.1
2017	1,079	325.5	808 (75)	1,297.8	227 (21)	174.2	44 (4)	31.7
2018	1,398	421.7	990 (71)	1,590.2	349 (25)	267.7	59 (4)	42.5
2019	1,577	475.7	1,056 (67)	1,696.2	419 (27)	321.4	102 (6)	73.4
2020	623	210.9	414 (66)	716.3	166 (27)	143.6	43 (7)	35.2
2021	1,657	560.9	946 (57)	1,636.8	517 (31)	447.1	194 (12)	159.0
2022	1,927	652.3	1,163 (60)	2,012.2	507 (26)	438.5	257 (13)	210.7
2023	2,334	790.1	1,420 (61)	2,456.9	650 (28)	562.1	264 (11)	216.4
Mean per annum*	**1,402**		**967 (69)**		**333 (24)**		**102 (7)**	

*Mean per annum excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic.
Source: Health Protection Surveillance Centre.

The notified RSV hospital admission case rates per 100,000 for those aged 0 to 4 years are presented by age band and year in Figure 4.8. Rates were consistently highest in infants aged less than one year. In general, the RSV hospital admission case rates have increased over time; however, as noted earlier, this may relate to improved ascertainment due to changes in RSV testing patterns rather than a true increase in burden.

Figure 4.8 Notified RSV hospital admission case rates per 100,000 for those aged 0 to 4 years in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

Table 4.5 provides an overview of the number and rate (per 100,000 population) of notified RSV hospital admissions for those aged 0 to 2 years for the 2022-2023 season. It is worth noting that this differs from the other HPSC admission data which were reported by calendar year. In considering the total population aged 0 to 2 years, infants aged less than one year accounted for 69% (n=1,124) of notified RSV hospital admissions, with 74% (n=834) of this burden in those aged less than six months (that is, 51% of all cases in those aged 0 to 2 years occurred in those aged less than 6 months).

Table 4.5 Number and rate (per 100,000 population) of notified RSV hospital admissions for those aged 0 to 2 years in Ireland (for the 2022-2023 season), reported by age band

Age group	Number (%)	Rate per 100,000
<6 months	834 (51)	2,886.0
≥6 months to <1 year	290 (18)	1,003.5
1-2 years	500 (31)	432.4
Total (0 to 2 years)	**1,624**	

Source: Health Protection Surveillance Centre.

Hospital discharges and bed days

Data from the HIPE system in Ireland were used to examine hospital discharges with and without an ICU stay for those aged 0 to 4 years with a primary or secondary diagnosis of RSV (with ICD-10 codes B97.4, J12.1, J20.5 and J21.0) or acute bronchiolitis (with ICD-10 codes J21.8 and J21.9). As noted in section 4.2, a HIPE discharge record is created when a patient is discharged from, or dies in, hospital. This record contains information for a discrete episode of care. An episode of care begins at admission to hospital, as a day or inpatient, and ends at discharge from (or death in) that hospital.[167] Data were provided by calendar year and are reported below separately for RSV and acute bronchiolitis.

RSV discharges and bed days (primary diagnosis)

Table 4.6 provides an overview of inpatient discharges with a primary diagnosis of RSV in those aged 0 to 4 years, from 2013 to 2022 presented by age band. In those aged 0 to 4 years, infants aged less than one year accounted for 90% of discharges with an ICU stay and 84% of discharges without an ICU stay. In infants aged less than one year, the mean annual number of discharges with and without an ICU stay was 109 (range: 56 to 186) and 1,128 (range: 674 to 1,869), respectively. On average, therefore, in infants aged less than one year, approximately 1 in 12 discharges included an ICU stay. This contrasts with the population aged 1 to 2 years, where approximately 1 in 21 discharges included an ICU stay during this period.

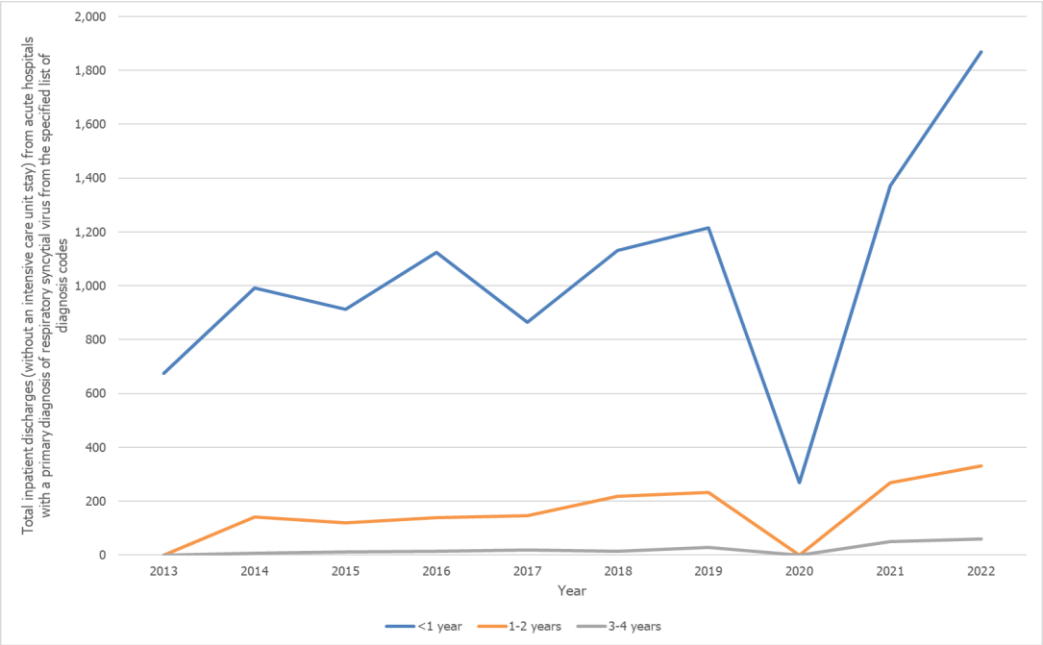
Table 4.6 Hospital discharges for those aged 0 to 4 years with a primary diagnosis of RSV (2013 to 2022) reported by age band

	Hospital discharges without an intensive care unit stay		Hospital discharges which included an intensive care unit stay	
Age band (years)	Total number of discharges* (% of total discharges ≤4 years)	Mean annual number of discharges* (range)	Total number of discharges* (% of total discharges ≤4 years)	Mean annual number of discharges* (range)
<1	10,152 (84)	1,128 (674-1,869)	979 (90)	109 (56-186)
1-2†	1,597 (13)	200 (120-330)	30 (3)	10 (6-13)
3-4†	200 (2)	25 (6-60)	0 (0)	0 (NA)
≤4~	**12,065**	**1,341 (790-2,259)**	**1,090**	**121 (62-201)**

Note: Hospital discharges associated with a primary diagnosis of RSV from the specified list of diagnosis codes.
*Total and mean exclude data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5, and or where an associated cell discloses the value of a suppressed cell. Further suppression of other cells may also be necessary.
†Where suppressed data were present, they were excluded when calculating summary statistics.
~Reported values are higher than the sum of discharges broken down by age band, as they include those cells suppressed for confidentiality when reported by age band.
Source: Hospital In-Patient Enquiry System.

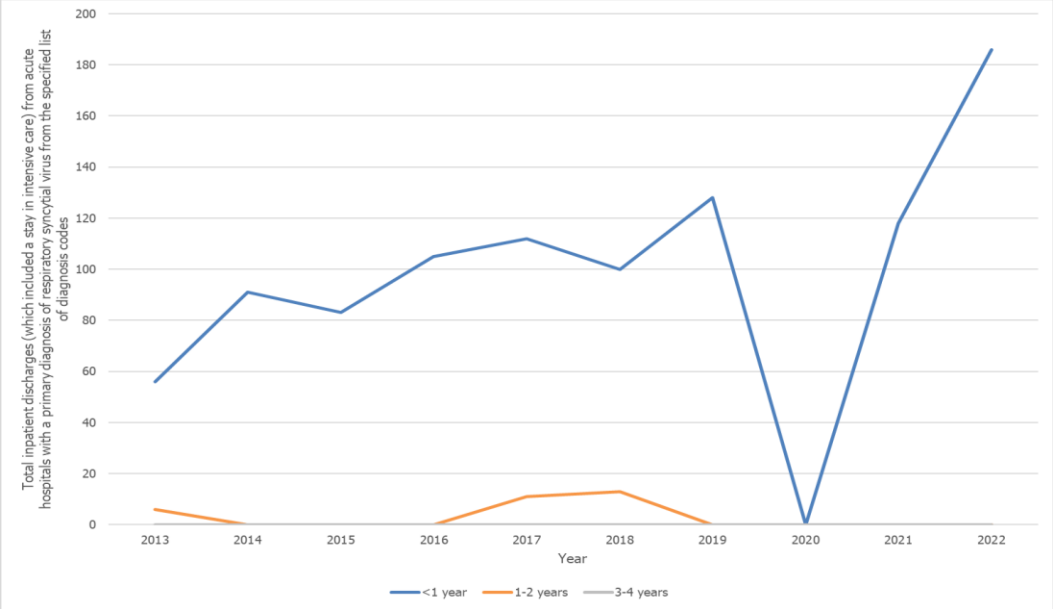
Figure 4.9 and Figure 4.10 present the above data graphically per year. As depicted, the number of hospital discharges with a primary diagnosis of RSV (regardless of whether the patient had a stay in ICU) was substantially higher in infants aged less than one year old. In general, RSV hospital discharge rates have increased over time, but as noted earlier, caution is required in inferring temporal trends based on the data presented given changes in RSV testing patterns.

Figure 4.9 Hospital discharges (without an intensive care unit stay) per calendar year for those aged 0 to 4 years with a primary diagnosis of RSV (2013 to 2022), reported by age band



Source: Hospital In-Patient Enquiry System.

Figure 4.10 Hospital discharges (which included an intensive care unit stay) per calendar year for those aged 0 to 4 years with a primary diagnosis of RSV (2013 to 2022) reported by age band



Note: For reasons of confidentiality, data for those aged three to four years are suppressed.
Source: Hospital In-Patient Enquiry System.

To estimate the distribution of RSV-related discharges across the RSV season, data were also obtained by yearly quarter. Table 4.7 provides an overview of inpatient discharges with a primary diagnosis of RSV in those aged 0 to 4 years, from 2017 to 2022, presented by yearly quarter. Hospital discharges in quarter four accounted for the greatest proportion of annual discharges, ranging from 71% in 2018 to 91% in 2021 of those without an ICU stay, and from 61% in 2018 to 91% in 2021 of those that included an ICU stay. Infants aged less than one year accounted for the greatest proportion of hospital discharges in quarter four each year, ranging from 81% in 2018 and 2019 to 83% in 2022 of quarterly discharges without an ICU stay, and from 85% in 2021 to 93% in 2022 of quarterly discharges which included an ICU stay. The proportion of quarterly discharges that occurred in each age band are not reported in Table 4.7 for reasons of confidentiality and the subsequent suppression of cells.

Table 4.7 Hospital discharges for those aged 0 to 4 years with a primary diagnosis of RSV (2017 to 2022) reported by quarter

Year	Quarter (Q)	Hospital discharges without an intensive care unit stay (% of annual discharges)	Hospital discharges with an intensive care unit stay (% of annual discharges)
2017	Q1	226 (22)	42 (34)
	Q2	23 (2)	- (-)
	Q3	21 (2)	0 (0)
	Q4	759 (74)	78 (63)
2018	Q1	337 (25)	37 (33)
	Q2	39 (3)	- (-)
	Q3	13 (1)	- (-)
	Q4	971 (71)	69 (61)
2019	Q1	364 (25)	29 (21)
	Q2	18 (1)	- (-)
	Q3	31 (2)	- (-)
	Q4	1,064 (72)	105 (76)
2021	Q1	- (-)	0 (0)
	Q2	- (-)	0 (0)
	Q3	143 (8)	12 (9)
	Q4	1,538 (91)	127 (91)
2022	Q1	71 (3)	10 (5)
	Q2	47 (2)	- (-)
	Q3	211 (9)	10 (5)
	Q4	1,930 (85)	176 (88)

Note: Hospital discharges associated with a primary diagnosis of RSV from the specified list of diagnosis codes. Quarterly data exclude data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5 (and replaced by -).
Source: Hospital In-Patient Enquiry System.

Table 4.8 reports the mean annual length of stay for those aged 0 to 4 years with a primary diagnosis of RSV (2013 to 2022). For reasons of confidentiality, data are suppressed when there are small numbers (1 to 5), with this issue particularly impacting data for those aged between 3 and 4 years. Across all age bands, the

mean annual length of stay associated with discharges with and without an ICU stay was 13 days (range: 8 to 25) and 4 days (range: 3 to 4), respectively. For those aged less than one year (who accounted for 90% and 84% of all discharges with and without and ICU stay, respectively (Table 4.6)), the mean annual length of stay for these discharges was 13 days (range: 7 to 27) and 4 days (range: 3 to 4), respectively.

Table 4.8 Annual hospital inpatient length of stay for those aged 0 to 4 years with a primary diagnosis of RSV (2013 to 2022) reported by age band

Age band (years)	Mean annual length of stay without an intensive care unit stay* (range)	Mean annual length of stay which included an intensive care unit stay* (range)
<1	4 (3-4)	13 (7-27)
1-2†	4 (3-5)	11 (6-14)
3-4†	6 (2-13)	0 (NA)
≤4~	**4 (3-4)**	**13 (8-25)**

Note: Hospital length of stay associated with a primary diagnosis of RSV from the specified list of diagnosis codes.
*Mean excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5, and or where an associated cell discloses the value of a suppressed cell. Further suppression of other cells may also be necessary.
†Where suppressed data were present, they were excluded when calculating summary statistics.
~Reported values include those cells suppressed for confidentiality when reported by age band.
Source: Hospital In-Patient Enquiry System.

Considering those aged 0 to 4 years with a primary diagnosis of RSV, for the period 2013 to 2022, there was, on average 1,341 (range: 790 to 2,259) discharges each year that did not include an ICU stay and 121 (range: 62 to 201) discharges each year that included an ICU stay. This corresponded to a mean of 4,874 (range: 3,118 to 7,377) bed days per annum and a mean annual cost of €10.4 million (range: €6 million to €17.5 million) for discharges that did not include an ICU stay, and a mean of 1,482 (range: 926 to 1,956) bed days per annum and a mean annual cost of €4.1 million (range: €2.6 million to €5.1 million) for discharges that included an ICU stay.

RSV discharges and bed days (secondary diagnosis)

Data were also sought in relation to inpatient discharges with a secondary diagnosis of RSV in those aged 0 to 4 years. For the period 2013 to 2022 (and excluding data for 2020 which was not considered representative due to the influence of COVID-19), there were on average 25 (range: 17 to 34) and 234 (range: 42 to 731) discharges each year with and without an ICU stay, respectively, in those aged 0 to

4 years. Considering specifically infants aged less than one year, there were on average 16 (range: 8 to 26) and 74 (range: 30 to 148) discharges each year with and without an ICU stay, respectively.

Acute bronchiolitis discharges and bed days (primary diagnosis)

As noted in section 4.3.1, while testing for RSV has increased in recent years, it is possible that not all individuals presenting with symptoms of RSV are tested and confirmed as a case. Children with acute RSV infection frequently present with bronchiolitis, with RSV noted as the most common cause of acute bronchiolitis in children. For context, data in relation to discharges with a primary diagnosis of bronchiolitis were also sought.

Table 4.9 provides an overview of inpatient discharges with a primary diagnosis of acute bronchiolitis in those aged 0 to 4 years, from 2013 to 2022 presented by age band. In those aged 0 to 4, infants aged less than one year accounted for 88% of discharges without an ICU stay and 64% of discharges with an ICU stay. The mean annual number of discharges (without an ICU stay) observed in this age band was 1,493 (range: 879 to 1,770), and the mean annual number of discharges (which included an ICU stay) was 40 (range: 27 to 66).

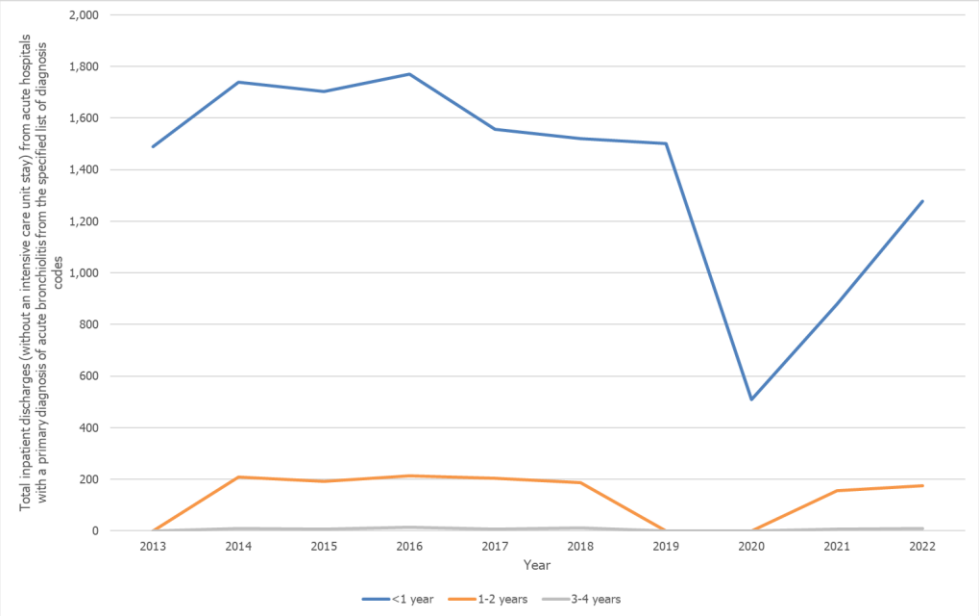
Table 4.9 Hospital discharges for those aged 0 to 4 years with a primary diagnosis of acute bronchiolitis (2013 to 2022) reported by age band

	Hospital discharges without an intensive care unit stay		Hospital discharges which included an intensive care unit stay	
Age band (years)	Total number of discharges* (% of total discharges ≤4 years)	Mean annual number of discharges* (range)	Total number of discharges* (% of total discharges ≤4 years)	Mean annual number of discharges* (range)
<1	13,439 (88)	1,493 (879-1,770)	280 (64)	40 (27-66)
1-2†	1,336 (9)	191 (155-214)	35 (8)	9 (6-14)
3-4†	66 (0)	9 (6-14)	0 (0)	0 (NA)
≤4~	**15,201**	**1,689 (1,042-1,998)**	**435**	**48 (30-81)**

Note: Hospital discharges associated with a primary diagnosis of acute bronchiolitis from the specified list of diagnosis codes.
*Total and mean exclude data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5, and or where an associated cell discloses the value of a suppressed cell. Further suppression of other cells may also be necessary.
†Where suppressed data were present, they were excluded when calculating summary statistics.
~Reported values are higher than the sum of discharges broken down by age band, as they include those cells suppressed for confidentiality when reported by age band.
Source: Hospital In-Patient Enquiry System.

Figure 4.11 presents the discharge data for those without an ICU stay by year. There appears to be a decrease in the number of discharges over time. When considered in tandem with the RSV discharge data, this may reflect that a higher proportion of children presenting with acute bronchiolitis are being tested for, and identified as having, RSV. When considering the combined burden associated with RSV and acute bronchiolitis cases reported per year from 2013 to 2022, overall, the proportion of cases coded as acute bronchiolitis has decreased from 67% in 2013 to 39% in 2022.

Figure 4.11 Hospital discharges (without an intensive care unit stay) per calendar year for those aged 0 to 4 years with a primary diagnosis of acute bronchiolitis (2013 to 2022) reported by age band



Source: Hospital In-Patient Enquiry System.

Table 4.10 provides an overview of inpatient discharges with a primary diagnosis of acute bronchiolitis in those aged 0 to 4 years, from 2017 to 2022, presented by yearly quarter. Following the trend observed for a primary diagnosis of RSV, for those without an ICU stay the highest proportion of hospital discharges occurred in quarter four, ranging from 40% to 68% of annual discharges. For those with an ICU stay, there was no clear pattern in the distribution of cases.

Table 4.10 Hospital discharges for those aged 0 to 4 years with a primary diagnosis of acute bronchiolitis (2017 to 2022) reported by quarter

Year	Quarter (Q)	Hospital discharges without an intensive care unit stay (% of annual discharges)	Hospital discharges with an intensive care unit stay (% of annual discharges)
2017	Q1	468 (27)	12 (40)
	Q2	276 (16)	6 (20)
	Q3	182 (10)	- (-)
	Q4	839 (48)	8 (27)
2018	Q1	528 (31)	11 (28)
	Q2	295 (17)	13 (33)
	Q3	143 (8)	- (-)
	Q4	755 (44)	11 (28)
2019	Q1	480 (29)	17 (27)
	Q2	221 (13)	9 (15)
	Q3	161 (10)	7 (11)
	Q4	823 (49)	29 (47)
2021	Q1	46 (4)	- (-)
	Q2	81 (8)	7 (18)
	Q3	205 (20)	12 (30)
	Q4	710 (68)	20 (50)
2022	Q1	293 (20)	21 (26)
	Q2	320 (22)	23 (28)
	Q3	264 (18)	13 (16)
	Q4	587 (40)	24 (30)

Note: Hospital discharges associated with a primary diagnosis of acute bronchiolitis from the specified list of diagnosis codes. Quarterly data exclude data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5 (and replaced by -).
Source: Hospital In-Patient Enquiry System.

4.4.3 Complications and hospitalisations (older adults)

RSV-related emergency department visits

Notified RSV ED visit rates per 100,000 for adults aged 65 years and older are reported in Table 4.11; data were only available for years 2018 to 2023. Again, it is noted that these data are reported by calendar year, rather than by RSV season. In those aged 65 years and older, the notified ED visit rate reported for 2022 (58.7 per 100,000) was the highest observed across all six years of data examined in the HTA. When disaggregated by five-year age band, notified ED visit rates typically increased with increasing age. For 2023, the data indicate notified ED visit rates of 31.1 per 100,000 (n=74) in those aged 65 to 69 years, 38.4 per 100,000 (n=78) in those aged 70 to 74 years, 55.8 per 100,000 (n=86) in those aged 75 to 79 years, 80.8 per 100,000 (n=78) in those aged 80 to 84 years, and 105.4 per 100,000 (n=89) in those aged 85 years and older. On average, adults aged 80 years and older accounted for 43% of all ED visits in this cohort (range: 40% to 46%). In those

aged 80 years and older, the notified case rate ranged from 16.6 to 115.5 per 100,000, in 2021 and 2022, respectively.

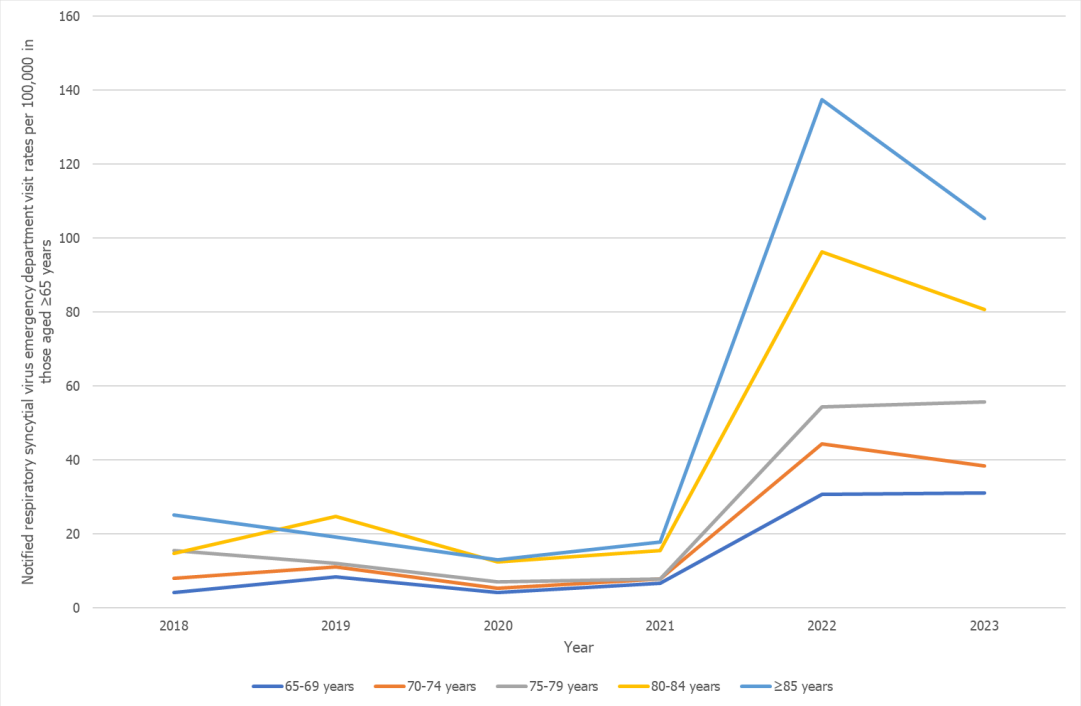
Table 4.11 Notified RSV emergency department visits in adults aged 65 years and older in Ireland, reported by age band

Year	≥65 years		65-69 years		70-74 years		75-79 years		80-84 years		≥85 years	
	N	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000
2018	69	10.8	9 (13)	4.3	13 (19)	8.0	18 (26)	15.6	12 (17)	14.8	17 (25)	25.2
2019	83	13.0	18 (22)	8.5	18 (22)	11.1	14 (17)	12.1	20 (24)	24.7	13 (16)	19.2
2020	55	7.1	10 (18)	4.2	11 (20)	5.4	11 (20)	7.1	12 (22)	12.4	11 (20)	13.0
2021	74	9.5	16 (22)	6.7	16 (22)	7.9	12 (16)	7.8	15 (20)	15.5	15 (20)	17.8
2022	456	58.7	73 (16)	30.7	90 (20)	44.4	84 (18)	54.5	93 (20)	96.3	116 (25)	137.4
2023	405	52.2	74 (18)	31.1	78 (19)	38.4	86 (21)	55.8	78 (19)	80.8	89 (22)	105.4
Mean per annum*	**217**		**38 (17)**		**43 (20)**		**43 (20)**		**44 (20)**		**50 (23)**	

*Mean per annum excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic.
Source: Health Protection Surveillance Centre.

The notified RSV ED visit rates per 100,000 for adults aged 65 years and older are presented by age band and year in Figure 4.12. Rates were highest in adults aged 85 years and older, in every year between 2018 and 2023 with the exception of 2019.

Figure 4.12 Notified RSV emergency department visit rates per 100,000 for adults aged 65 years and older in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

RSV-related hospital admissions

Notified RSV hospital admission rates per 100,000 for adults aged 65 years and older are reported in Table 4.12. In those aged 65 years and older, the notified hospital admission rate reported for 2022 (74.6 per 100,000) was the highest observed across all 11 years of data examined in the HTA. Rates of hospital admissions generally increased with increasing age and were consistently highest in those aged 85 years and older. For 2023, notified hospital admission rates were 24.9 per 100,000 (n=70) in those aged 65 to 69 years, 43.4 per 100,000 (n=88) in those aged 70 to 74 years, 63.5 per 100,000 (n=98) in those aged 75 to 79 years, 118.0 per 100,000 (n=114) in those aged 80 to 84 years, and 168.2 per 100,000 (n=142) in those aged 85 years and older. On average, adults aged 80 years and older accounted for 46% of all hospital admissions in this cohort (range: 29% to 50%). In those aged 80 years and older, the notified case rate ranged from 2.0 to 151.9 per 100,000, in 2014 and 2022, respectively.

Table 4.12 Notified RSV hospital admissions for adults aged 65 years and older in Ireland, reported by age band

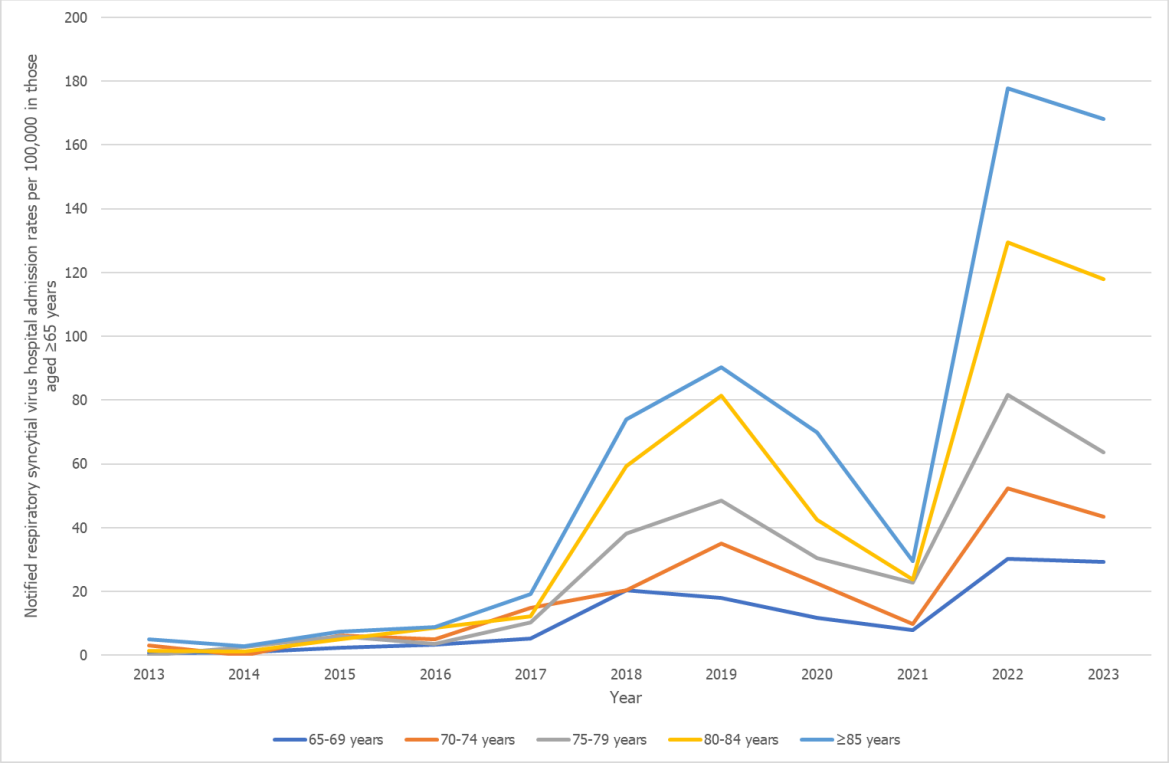
Year	≥65 years		65-69 years		70-74 years		75-79 years		80-84 years		≥85 years	
	N	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000	n (%)	Rate per 100,000
2013	9	1.7	1 (11)	0.6	4 (44)	3.0	0 (0)	0.0	1 (11)	1.4	3 (33)	5.1
2014	8	1.3	2 (25)	0.9	0 (0)	0.0	3 (38)	2.6	1 (13)	1.2	2 (25)	3.0
2015	31	4.9	5 (16)	2.4	10 (32)	6.2	7 (23)	6.1	4 (13)	4.9	5 (16)	7.4
2016	32	5.0	7 (22)	3.3	8 (25)	4.9	4 (13)	3.5	7 (22)	8.6	6 (19)	8.9
2017	70	11.0	11 (16)	5.2	24 (34)	14.8	12 (17)	10.4	10 (14)	12.3	13 (19)	19.2
2018	218	34.2	43 (20)	20.4	33 (15)	20.3	44 (20)	38.1	48 (22)	59.2	50 (23)	74.0
2019	278	43.6	38 (14)	18.0	57 (21)	35.1	56 (20)	48.5	66 (24)	81.4	61 (22)	90.3
2020	221	28.5	28 (13)	11.8	46 (21)	22.7	47 (21)	30.5	41 (19)	42.4	59 (27)	69.9
2021	122	15.7	19 (16)	8.0	20 (16)	9.9	35 (29)	22.7	23 (19)	23.8	25 (20)	29.6
2022	579	74.6	72 (12)	30.2	106 (18)	52.2	126 (22)	81.7	125 (22)	129.4	150 (26)	177.6
2023	512	66.0	70 (14)	29.4	88 (17)	43.4	98 (19)	63.5	114 (22)	118.0	142 (28)	168.2
Mean per annum*	**186**		**27 (15)**		**35 (19)**		**39 (21)**		**40 (22)**		**46 (25)**	

*Mean per annum excludes data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic.

Source: Health Protection Surveillance Centre.

The notified RSV hospital admission case rates per 100,000 for those aged 65 years and older are presented by age band and year in Figure 4.13. As noted, rates generally increased with increasing age and were consistently highest in those aged 85 years and older. In general, there appears to be a trend of increasing hospital admission case rates over time. However, as already highlighted, there has been a substantial increase in testing capacity since 2016, and changes in testing patterns since the COVID-19 pandemic (such as increased use of multiplex RT-PCR testing), both of which could also have an impact on RSV hospital admission rates. Caution is therefore required in inferring temporal trends based on the data presented.

Figure 4.13 Notified RSV hospital admission case rates per 100,000 for adults aged 65 years and older in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

Hospital discharges and bed days

Data from the HIPE system in Ireland were used to examine hospital discharges with and without an ICU stay for patients aged 65 years and older with a primary or secondary diagnosis of RSV (with ICD-10 codes B97.4, J12.1, J20.5 and J21.0). Data were provided by calendar year.

RSV discharges and bed days (primary diagnosis)

Considering discharges for those with a primary diagnosis of RSV that did not include an ICU stay, Table 4.13 provides an overview of the number of discharges and the associated length of stay for adults aged 65 years and older for the period from 2013 to 2022. Overall, the number of discharges was relatively low with a total of 225 discharges over this time period, of which 134 were recorded in 2022. Similarly, when considering the number of associated bed days, there were a total of 2,154 bed days over this time period, of which 1,302 occurred in 2022. Accordingly, the mean annual cost associated with these discharges was €0.4 million, although as noted, these data are highly skewed (range: €0 to €1.3 million). Adults aged 80 years and older accounted for 48% of total discharges in this cohort. Adults aged 85 years and older accounted for the highest proportion of discharges (28%), the highest mean annual number of discharges (n=11), and the longest mean length of stay (6 days (range: 0 to 15)). Discharges that included an ICU stay were uncommon, with fewer than six discharges a year recorded in those aged 65 years and older in all but one of the years over this time period.

Table 4.13 Total hospital discharges and length of stay (for discharges that did not include an ICU stay) in adults aged 65 years and older with a primary diagnosis of RSV (2013 to 2022) reported by age band

Age band (years)	Total number of discharges* (% of total discharges ≥65 years)	Mean annual number of discharges* (range)	Mean annual length of stay in days* (range)
65-69†	30 (13)	6 (0-24)	2 (0-7)
70-74†	36 (16)	5 (0-18)	5 (0-9)
75-79†	35 (16)	6 (0-27)	4 (0-11)
80-84†	43 (19)	7 (0-25)	5 (0-10)
≥85†	64 (28)	11 (0-40)	6 (0-15)
≥65~	**225**	**45 (0-134)**	**8 (0-13)**

Note: Hospital discharges associated with a primary diagnosis of RSV from the specified list of diagnosis codes.
*Total and mean exclude data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5, and or where an associated cell discloses the value of a suppressed cell. Further suppression of other cells may also be necessary.
†Where suppressed data were present, they were excluded when calculating summary statistics.
~Reported values include those cells suppressed for confidentiality when reported by age band.
Source: Hospital In-Patient Enquiry System.

RSV discharges and bed days (secondary diagnosis)

Table 4.14 provides an overview of inpatient discharges with a secondary diagnosis of RSV in those aged 65 years and older, from 2013 to 2022 presented by age band. Adults aged 75 to 79 years accounted for the greatest proportion of discharges (18%) and the highest mean annual number of discharges (n=30), for those without an ICU stay. The mean annual number of discharges (without an ICU stay) observed in this age band was 30 (range: 0 to 110). Similar to discharges without an ICU stay, discharges that included an ICU stay were highest in those aged 75 to 79 years; the mean annual number of discharges (with an ICU stay) was 8 (range: 0 to 15).

Table 4.14 Hospital discharges for adults aged 65 years and older with a secondary diagnosis of RSV (2013 to 2022) reported by age band

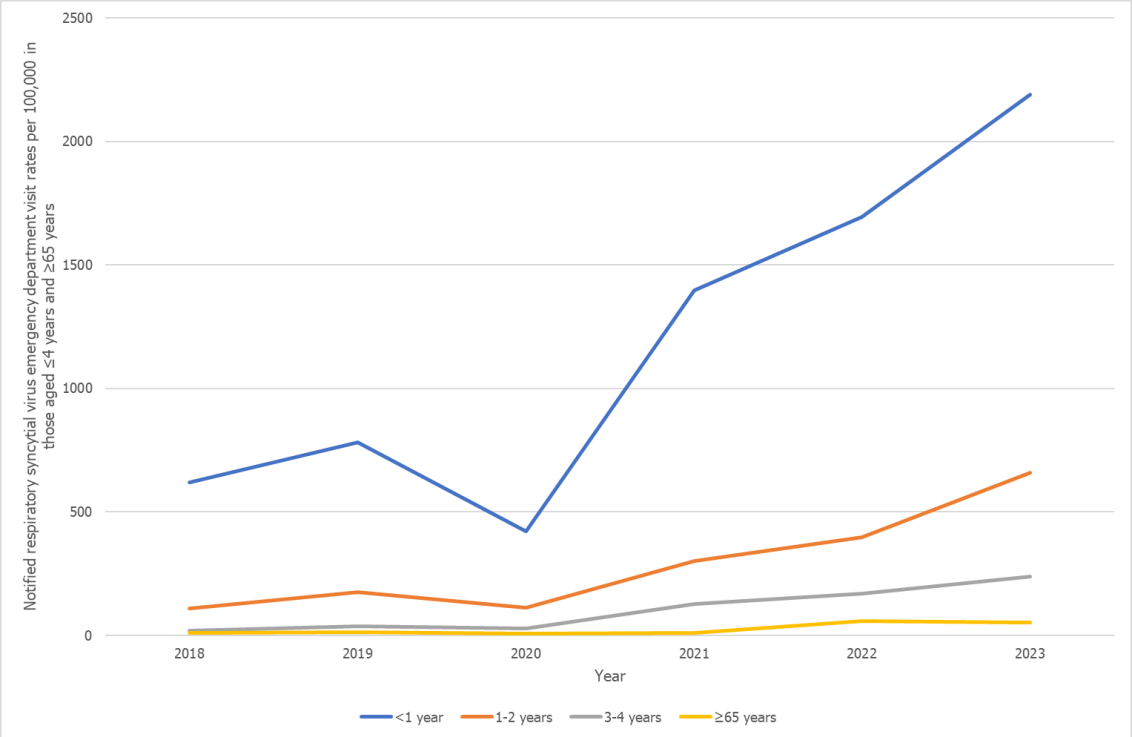
	Hospital discharges without an intensive care unit stay		Hospital discharges which included an intensive care unit stay	
Age band (years)	Total number of discharges* (% of total discharges ≥65 years)	Mean annual number of discharges* (range)	Total number of discharges* (% of total discharges ≥65 years)	Mean annual number of discharges* (range)
65-69†	70 (8)	18 (0-70)	16 (15)	4 (0-16)
70-74†	138 (16)	28 (0-102)	18 (16)	6 (0-12)
75-79†	149 (18)	30 (0-110)	31 (28)	8 (0-15)
80-84†	All data suppressed	All data suppressed	0 (0)	0 (NA)
≥85†	73 (9)	12 (0-33)	0 (0)	0 (NA)
≥65~	**851**	**170 (6-543)**	**110**	**22 (7-58)**

Note: Hospital discharges associated with a secondary diagnosis of RSV from the specified list of diagnosis codes.
*Total and mean exclude data from 2020 which are not considered representative due to the influence of the COVID-19 pandemic. For reasons of confidentiality, counts are suppressed for cells where the number of discharges is between 1 and 5, and or where an associated cell discloses the value of a suppressed cell. Further suppression of other cells may also be necessary.
†Where suppressed data were present, they were excluded when calculating summary statistics.
~Reported values are higher than the sum of discharges broken down by age band as they include those cells suppressed for confidentiality when reported by age band.
Source: Hospital In-Patient Enquiry System.

4.4.4 Comparison of complications and hospitalisations in those aged 0 to 4 years and older adults

The notified RSV ED visit rates per 100,000 for those aged less than 4 years and adults aged 65 years and older are presented by age band and year in Figure 4.14. As depicted, the rate of ED visits per 100,000 is considerably higher in infants aged less than one year compared with all other age bands. In 2023, there were 1,266 ED visits in those aged less than one year compared with 405 ED visits in those aged 65 years and older.

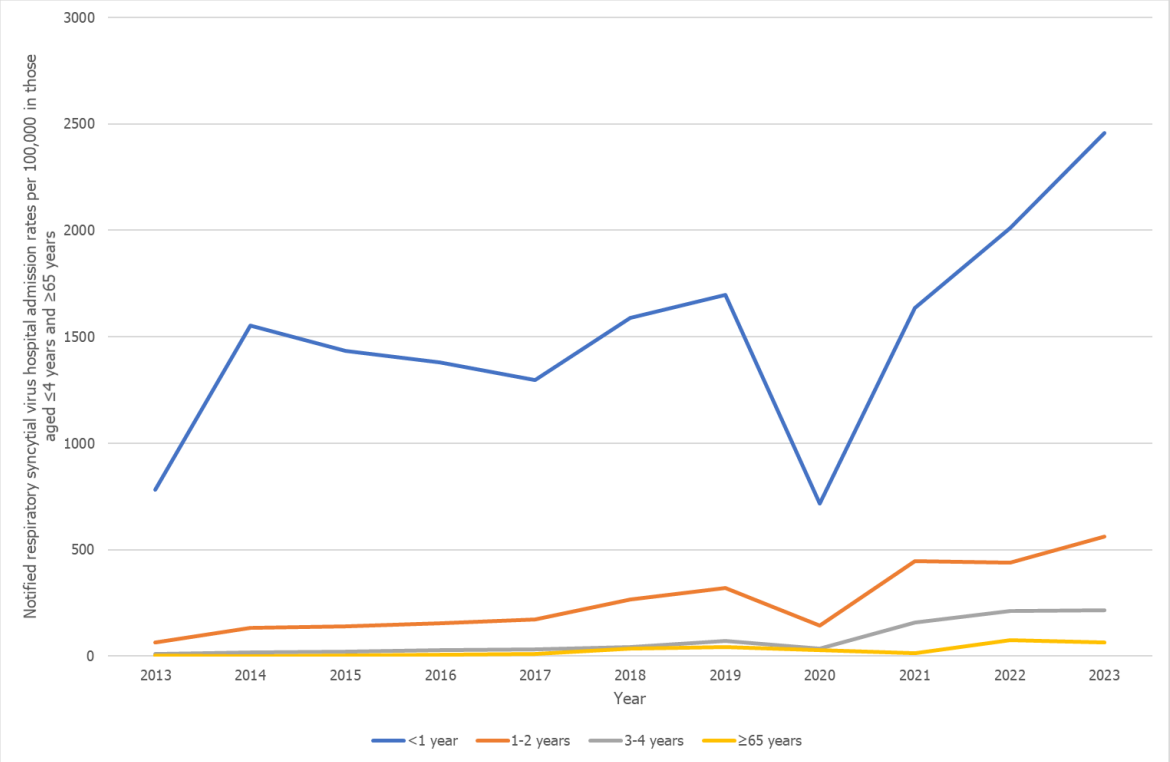
Figure 4.14 Notified RSV emergency department visit rates per 100,000 for those aged 0 to 4 years and adults aged 65 years and older in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

The notified RSV hospital admission rates per 100,000 for those aged 0 to 4 years and adults aged 65 years and older are presented by age band and year in Figure 4.15. Consistent with the picture for ED visits, the rate of hospital admissions per 100,000 is considerably higher in infants aged less than one year compared with all other age bands. For 2023, there were 1,420 admissions in those aged less than one year compared with 512 admissions in those aged 65 years and older.

Figure 4.15 Notified RSV hospital admission case rates per 100,000 in those aged 0 to 4 years and adults aged 65 years and older in Ireland, reported by age band and year



Source: Health Protection Surveillance Centre.

Similar patterns were seen when considering hospital discharge data with a disproportionate burden seen in children aged 0 to 4 years compared with adults aged 65 years and older, with a markedly higher burden seen in children aged less than one year compared with all other age groups. This was evident in terms of hospital discharges for those aged less than one year and those aged 65 years and older with a primary diagnosis of RSV (1,869 vs. 134 for discharges without an ICU stay and 186 vs. 10 for discharges that included an ICU stay respectively in 2022). Similarly, when considering the total bed days associated with these discharges, in 2022 there were a total of 7,377 vs. 1,302 for discharges that did not include an ICU stay and 1,686 vs. 179 bed days for discharges that included an ICU stay, for those aged less than one year and those aged 65 years and older, respectively. When considering all discharge data associated with RSV (primary and secondary diagnoses), a higher proportion of the discharges in those aged 65 years and older relate to a secondary diagnosis of RSV, whereas these account for a small proportion of all discharges in those aged 0 to 4 years. As identified in sections 4.4.1 and 4.4.2, while recognising that there has been some year-on-year variability, the burden of RSV appears to have increased over time; however, this may relate to changes in

RSV testing patterns leading to improved case ascertainment rather a true increase in burden.

4.4.5 Mortality in Ireland

Most patients experience uncomplicated illness secondary to RSV infection, but some develop severe disease which can be characterised by the worsening of chronic conditions (such as asthma and chronic obstructive pulmonary disease); short, shallow and rapid breathing; wheezing; cyanosis (blue-purple discolouration of the skin, lips or tongue due to lack of oxygen); and in some cases death.[192] RSV-related mortality data were obtained from the HIPE.

Children (aged 0 to 4 years)

Data in relation to deaths associated with a primary or secondary diagnosis of RSV, and for those with acute bronchiolitis, were obtained for those aged 0 to 4 years for the period 2013 to 2022. Mortality rates have been consistently low in those with a primary (range: 0.0 to 0.9 per 100,000) or secondary (range: 0.0 to 0.7 per 100,000) diagnosis of RSV and similarly in those with a primary diagnosis of acute bronchiolitis (range: 0.0 to 0.9 per 100,000). In terms of absolute numbers, since 2013 there has been a mean of one RSV-related death annually for those with a primary diagnosis of RSV (range: 0 to 3), for those with a secondary diagnosis of RSV (range: 0 to 2) and for those with a primary diagnosis of acute bronchiolitis (range: 0 to 3).

Older adults (aged 65 years and older)

RSV mortality data for those with a primary or secondary diagnosis of RSV were obtained for adults aged 65 years and older for the period 2013 to 2022. The majority of data for those with a primary diagnosis of RSV were suppressed due to small count numbers (between 1 and 5 deaths per annum), with no deaths reported in 2013. The highest observed RSV-related mortality rate was reported in 2022 (2.4 per 100,000; n=19).

For those with a secondary diagnosis of RSV, since 2013 (excluding 2020) there has been a mean of 13 RSV-related deaths annually (range: 1 to 56). The highest observed mortality rate was reported for 2022 (7.2 per 100,000) with the absolute number of deaths in that year (n=56) substantially higher than in any of the preceding years (range: 1 to 15).

4.4.6 Burden of disease in EU/EEA countries and the UK

The joint ECDC-WHO/Europe database, the European Surveillance System (TESSy), collects respiratory virus activity in the 53 countries and areas with routine respiratory surveillance systems in the WHO/Europe Region. This data is hosted on

the European Respiratory Virus Surveillance Summary (ERVISS) since October 2023.[193] Through the HPSC, Ireland contributes to these data and reports on laboratory-confirmed RSV-positive cases. These ECDC data are not disaggregated for children aged 0 to 4 years, or adults aged 65 years and older.

A 2023 UK surveillance report indicated that in English secondary care, a total of 2,435 confirmed RSV cases were reported (across both hospital and critical care) from 35 participating sentinel trusts, between week 40/2022 and week 15/2023.[182] The cumulative RSV hospitalisation admission rate for the 2022-2023 season was 32.18 per 100,000 hospital trust catchment population. This hospital admission rate was higher than those observed in the previous pandemic seasons (2021-2022: 19.1 per 100,000; 2020-2021: 0.3 per 100,000).[182] However, cumulative RSV hospital admission rates in pre-pandemic seasons were higher than those reported during pandemic seasons, with rates of 48.2, 41.7 and 45.3 per 100,000, for 2019-2020, 2018-2019 and 2017-2018, respectively. These data were not disaggregated by age.[182]

Children (aged 0 to 4 years)

A 2023 study investigating age-specific estimates of RSV-associated hospitalisations in children less than five years[194] estimated that an average of 10 children per 1,000 living in the EU are hospitalised due to RSV annually (average rates in children under five years, 10.06 [95% CI: 9.9 to 10.2] per 1,000 population).[194] RSV-associated hospitalisation estimates from eight countries (six RESCEU project countries [REspiratory Syncytial virus Consortium in Europe][195] and two countries identified in the literature) were applied to country estimates across the wider European region. It is noted that RSV-associated hospitalisations included any admission that mentioned a respiratory tract infection (RTI), any pathogen-coded RTI admission, and or any RSV-coded RTI admission. Estimates were based on hospitalisations across the 1997 to 2018 period. An average of 245,244 (95% CI: 224,688 to 265, 799) RSV-associated hospital admissions was estimated, across the 27 EU countries and the UK, per year, in children less than five years. The majority of these cases were identified to occur among infants aged less than one year (74.9%).[194]

A 2022 RESCEU retrospective analysis of hospital admissions in seven European countries estimated that, annually, RSV-RTI hospital admissions accounted for 9.9 (95% CI: 9.8 to 10.0) to 21.2 (95% CI: 21.1 to 21.3) bed days per 1,000 children aged less than five years.[196] An RSI-RTI admission was identified as any admission which included a mention of RTI and RSV in the associated ICD-10 diagnosis codes. The majority of bed days were in infants aged under one year (range of 70% to 89% across the included countries). Hospital length of stay (LOS) for RSV-RTI in

children less than five years ranged from two days (interquartile range (IQR): 0.5 to 4 days) to four days (IQR: 2 to 6 days) across the countries included.[196] A 2024 retrospective analysis of German RSV hospitalisations between 2010 and 2019 (defined as a primary discharge diagnosis of an RSV ICD-10 code) reported a similar LOS in children aged less than five years (infants less than one year, median (IQR): 5 days (3 to 7 days); children aged 1 to 4 years, median (IQR): 4 days (3 to 6 days).[197]

In regards to RSV hospitalisation during the pandemic period, a 2024 meta-analysis including 61 studies from 19 countries estimated the annualised hospitalisation burden of RSV-associated acute lower respiratory infection (ALRI) in children aged less than five years.[198] In high-income countries, this rate decreased from 5.0 (95% UI: 3.6 to 6.8) per 100,000 in the 2019 calendar year to 1.0 (95% UI: 0.2 to 4.3) per 100,000, for the same time interval in 2020. Hospitalisation rates then increased in the 2021 calendar year (4.5 [95% UI: 2.6 to 7.7] per 100,000), and were similar (albeit slightly higher) to pre-pandemic rates for the April 2021-March 2022 period (6.0 [95% UI: 5.4 to 6.8] per 100,000).

A 2023 systematic analysis of Global Burden of Disease (GBD) 2019 data outlined that internationally, the RSV mortality rate for children aged 0 to 4 years declined from 65.54 (95% Uncertainty Interval (UI): 28.37 to 110.42) per 100,000 in 1990, to 18.68 (95% UI: 8.20 to 31.96) per 100,000 in 2019.[199] This decline in mortality has been attributed to successful initiatives targeted at children aged under 5 years, including increased education around preventable RSV risk factors (such as low birth weight and malnutrition), and pharmacological interventions (such as palivizumab) in preterm infants.[199]

Older adults (aged 65 years and older)

A 2023 RESCEU retrospective analysis of hospital admissions was conducted for adults aged 18 years or older, with RSV-associated hospitalisation estimates from six RESCEU project countries included.[200] When extrapolated to 28 EU countries (including the UK), an average of 145,102 (95% CI: 129,961 to 160,242) RSV-associated hospital admissions was estimated per year in adults aged 65 years and older.[200] Additionally, a higher rate of RSV-associated hospital admission was estimated in those aged 85 years and older (3.0 [95% CI: 2.6 to 3.4] per 100,000), compared with their younger counterparts (persons aged 75 to 84 years: 2.2 [95% CI: 2.1 to 2.4] per 100,000; persons aged 65 to 74 years: 0.66 [95% CI: 0.6 to 0.8] per 100,000). However, a 2023 systematic review and modelling study of RSV hospitalisation burden in older adults in high-income countries estimated that true RSV-associated hospitalisation burden may be over twice as high as that reported in

existing studies.[201] The current underestimation within the literature was attributed to variations in clinical specimens and RSV testing approaches.[201]

A 2024 retrospective analysis of German RSV hospitalisations between 2010 and 2019 (defined as a primary discharge diagnosis of an RSV ICD-10 code) estimated a median length of stay of eight days when considering all adults aged 60 years and older. When further stratified by age band (60 to 69 years, 70 to 79 years, 80 to 89 years, and 90 years and older), estimated IQRs were 5 to 12 days, 5 to 11 days, 6 to 11 days and 5 to 11 days, respectively.[197]

While a 2023 systematic analysis of GBD 2019 data did not report disaggregated data for adults aged 65 years and older, they noted that adults aged 70 years and older had the highest RSV mortality rate (34.5 [95% UI: 9.8 to 75.4] per 100,000), of all age bands included.[199] It was also noted that the global mortality rate ratio between those aged 70 years and older, and children aged 0 to 4 years, increased from 0.6 in 1990 to 1.9 in 2019, indicating a greater burden of RSV among the elderly in recent years.[199] A 2022 systematic review and meta-analysis, including 16 observational studies and a total of 762,084 older participants (60 years and older), suggested that the mortality rate attributable to RSV in older adults was similar to that of influenza.[202]

4.4.7 Wider burden of RSV

While the impact of RSV infection in Ireland and in the EU/EEA on hospitalisation and ED visits is well described (see sections 4.4.2, 4.4.3 and 4.4.6), the wider burden of RSV, such as that on families, carers, and primary healthcare resources (such as GPs) has not been fully explored. There are currently no Irish data available regarding the wider burden of RSV, and therefore a brief overview of relevant literature has been included below.

Children (aged 0 to 4 years)

A 2024 observational study in four European countries investigated the burden of RSV-induced hospitalisations in children aged less than 24 months on parental health-related quality of life (HR-QoL) and family functioning during the acute infection phase (n=138 respondents) and six weeks later (n=59 respondents).[203] Results identified that the hospitalisations negatively impacted parental and or carer HR-QoL. While scores significantly improved following the acute infection, over a quarter of caregivers still reported a persistent burden on their lives at six weeks. Among 31.3% of parents or carers included in the study that were in full or part time employment, 40.5% of these indicated that their job productivity was "very much" influenced by the hospitalisation of their child due to RSV, with an average of 29 working hours missed during the initial hospitalisation and 13.5 missed working hours following discharge.[203] Similarly, in infants and children with a history of

prematurity (a gestational age of less than 36 weeks), carers of those hospitalised due to RSV were noted to have significantly higher distress and anxiety compared with carers of age-matched controls. Again, while decline in caregiver anxiety was noted post discharge, it remained significantly higher than that of carers of control subjects two months post discharge.[204] Family health and functioning including family cohesion and adaptability were also noted to be significantly poorer while the child was hospitalised and post discharge, compared with values for the matched controls.[204] While not specific to RSV, a 2022 systematic review of mixed methods studies on parent experiences in relation to bronchiolitis outlined that parents (predominantly mothers) felt isolated, uninformed and misunderstood by healthcare professionals in regards to their child's diagnosis.[205] Limited data were identified in relation to care in the community; however, caregivers were noted to commonly experience negative emotional, time, and health impacts related to their child's hospitalisation.[205]

Regarding the burden on primary care, recent evidence is available from the RESCEU multicentre, prospective observational birth cohort study which included data from healthy term-born (≥37 weeks gestation) infants (n=9,154) across five European countries, which aimed to determine the healthcare burden of RSV in the first year of life. This study included a nested active surveillance cohort (n=993) to determine the incidence of medically-attended RSV infections. The incidence of symptomatic RSV infection confirmed by any diagnostic assay was 26.2% (95% CI 24.0 to 28.6) and that of medically-attended RSV infection was 14.1% (95% CI 12.3 to 16.0).[206, 207] A 2019 prospective, population-based study in the Finnish community followed 923 infants for the presence of acute respiratory infections (ARIs) from birth to 24 months of age.[208] Parents completed daily symptom diaries where all respiratory symptoms, any associated healthcare use (such as GP visits), and any absence from day-care or employment (for the parent) were noted. During the 24-month period, 42 children attending day-care who had an ARI, tested positive for RSV infection. This infection resulted in a significantly greater number of days absent from day-care, compared to those children with an ARI who did not test positive for RSV (median: 3 days versus 1 day; $p < 0.001$). Similarly, parents of children attending day-care, whose child tested positive for RSV, were absent from work for more days than parents of children who had an ARI but did not test positive for RSV (median: 2 days versus 0 days; $p < 0.001$).

Older adults (aged 65 years and older)

A 2021 qualitative, retrospective cross-sectional study reported on the experience of adults aged 50 years or older (n=30) with a history of PCR-confirmed RSV infection, eight of whom had been hospitalised or treated in the ED. Based on interviews undertaken between one and six months following testing, all participants reported

impacts on daily activities and or productivity, social activities and relationships during RSV infection.[209] This included struggling to complete tasks, being unable to attend social events and avoiding others.[209] A third of participants included within this study were employed, with all of these reporting a major impact on work due to RSV, including time off work and reduced productivity and efficiency.[209] However, it should be noted that this study may be at high risk of bias due to the small sample size, use of retrospective data collection six months post RSV infection and pharmaceutical industry funding.

4.5 Treatment for RSV

RSV infection is characterised by respiratory and systemic symptoms including fever, cough, wheezing, decreased appetite, sore throat and nasal congestion.[24] In most healthy individuals, symptoms of RSV infection are mild, self-limiting and typically resolve fully in two to three weeks. Individuals with mild symptoms may not require treatment or need to see their GP.[210] However, certain individuals have an increased risk of severe disease and may require hospitalisation. These high-risk groups include those with a weakened immune system, infants, young children and those aged 65 years or older.[210]

There is currently no specific medicine to treat RSV infection or shorten the duration of symptoms. For all ages, treatment for RSV is mainly supportive, aiming to ensure adequate oxygenation, ventilation, nutrition, and hydration. Approaches to treatment vary for infants and older adults, and depend on illness severity.[211] As already mentioned in section 2.4, the marketing authorisation for ribavirin was withdrawn on 22 June 2021 for commercial reasons, and therefore it is no longer authorised for use in Ireland.

Children (0 to 4 years)

Infants and young children (that is, aged 0 to 4 years) who show mild symptoms of RSV infection can usually be treated at home.[24] This includes rest, staying home from childcare and other activities until well enough to attend, and ensuring adequate nutrition and hydration. Infants and young children with symptoms of RSV infection should be monitored closely and medical care should be sought if their symptoms worsen. GP care should be sought immediately for infants with symptoms of RSV infection who were born prematurely (before 37 weeks), are aged less than two months, have heart or lung disease and or have an immune deficiency.[24]

Immediate hospital care is recommended for infants with any of the following symptoms:[24, 212, 213]

- apnoea (gaps in breathing of 5 to 10 seconds or more)

- severe respiratory distress (for example grunting, marked chest recession, or a respiratory rate of more than 70 breaths per minute)
- persistent oxygen saturation below 92%
- inadequate oral fluid intake or signs of dehydration (for example, having a dry nappy for 12 hours or more)
- cyanosis
- appears to be seriously unwell (for example, appears pale and sweaty, or has difficulty staying awake or waking up).

Treatment in hospital consists of supportive care measures that aim to stabilise the infant and alleviate symptoms, such as:[211-213]

- supplemental oxygen and respiratory support
- treatments to facilitate airway clearance (for example, administration of nebulised hypertonic saline or use of nasal suctioning)
- administration of fluids by nasogastric or orogastric tubes, or intravenously, if the infant cannot take sufficient fluid by mouth
- feeding support (nutrition delivered via nasogastric or orogastric tubes).

After discharge from hospital, parents or carers should be provided with information on how to recognise any further deterioration in symptoms and how to contact appropriate professionals, if required.[212] Antibiotics are not recommended for infants or children who have a persistent cough after RSV infection.[24]

Older adults (aged 65 years and older)

For healthy adults, symptoms of RSV infection are usually self-limiting and may be treated at home. The HSE recommends seeking advice from a pharmacist regarding over-the-counter medicines that may be used to alleviate symptoms.[24]

The HSE also recommends that adults with symptoms of RSV infection should seek emergency medical care if they have any of the following:

- difficulty breathing
- cyanosis
- apnoea
- increased respiratory rate (more than 60 breaths per minute)
- appear pale and sweaty, or cannot stay awake or wake up
- have heart or lung disease and symptoms of RSV infection
- have a weakened immune system and symptoms of RSV infection.[24]

Treatment in hospital for adults usually consists of supportive care measures, including supplemental oxygen, intravenous fluids, and antipyretics. Older adults, adults with comorbidities, or those with immune deficiency may experience severe

illness and require treatment in an intensive care unit — for example, for respiratory support and nutritional support.[211] Medicines that may be considered when treating symptoms of RSV infection in certain populations include bronchodilators for patients with asthma or chronic obstructive pulmonary disease, or antiviral therapy for patients with immune deficiency.[211]

4.6 Immunisation uptake rates

4.6.2 Immunisation uptake rates in Ireland

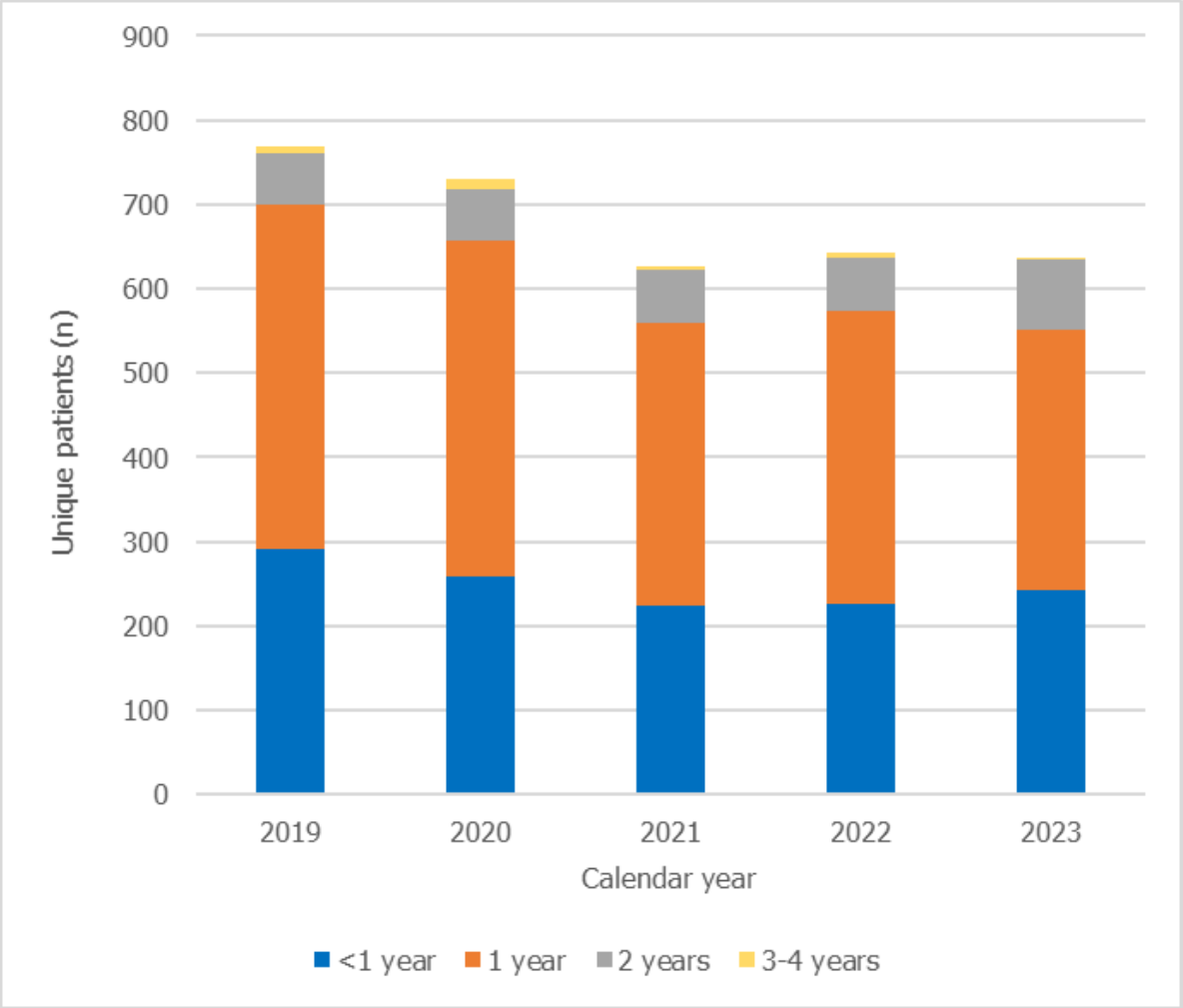
As outlined in Chapter 2, in Ireland immunoprophylaxis against RSV is not currently offered to healthy children and adults.[24] While palivizumab (Synagis®), which offers passive immunisation against RSV, is currently funded by the HSE, this is offered only to specified paediatric populations who are considered at high risk of serious RSV-related lower respiratory tract disease. Recently, a number of products have been authorised in Europe for active and passive immunisation against RSV in infants and older adults, including nirsevimab (Beyfortus®),[8] RSVpreF (Abrysvo®),[9] and RSVPreF3 (Arexvy®).[10] As described in Chapter 3, internationally, countries are currently assessing data related to these new technologies to generate recommendations regarding the inclusion of RSV in national immunisation schedules.

However, gaps in immunisation coverage exist across nearly all national immunisation programmes worldwide.[214] To gain an understanding of immunisation uptake rates in Ireland, quantitative data for infants, pregnant women and older adults were identified and described, where available. This was followed by a brief overview of relevant literature, aimed at understanding the drivers and barriers to immunisation uptake in these groups. This may provide insight into current immunisation-related behaviours in Ireland.[214]

Children (aged 0 to 4 years)

In Ireland, palivizumab is currently recommended to specific groups of children considered to be at high risk of severe RSV disease in their first and second years of life.[11] The total number of children in Ireland eligible to receive palivizumab each year is unknown, therefore palivizumab uptake rates are unknown. However, data obtained from the Primary Care Reimbursement Service (PCRS) for the years 2019 to 2023 indicate the annual number of unique patients aged 0 to 4 years in receipt of palivizumab in the community (Figure 4.16), ranging from 627 in 2021 to 768 in 2019. However, data for 2021 may not be representative due to the influence of the COVID-19 pandemic.

Figure 4.16 Number of unique patients aged 0 to 4 years to whom palivizumab was dispensed in community pharmacies in Ireland from 2019-2023, presented by age band and year



Source: Primary Care Reimbursement Service.

In addition to the numbers of unique patients, the numbers of unique prescriptions for palivizumab claimed for by community pharmacists from the PCRS each year are presented in Table 4.15. Children aged less than two years accounted for the majority of patients who received palivizumab across the reporting period (average proportions for 2019 to 2023 inclusive, aged less than 1 year: 36.5%; aged 1 year: 52.8%; aged 2 years: 9.6%; aged 3 to 4 years: 1.0%).

It is worth noting that these data most likely underestimate the total number of palivizumab doses prescribed and administered each year in Ireland, as PCRS data do not include doses of palivizumab administered in hospital settings. Children commencing palivizumab typically receive an initial dose in hospital, with subsequent doses delivered in community settings. Equally, for eligible children who experience long hospital stays during the RSV season, multiple doses of palivizumab that may

be administered in hospital are not included in PCRS data. On the other hand, the available data are reported by calendar year, rather than by RSV season. As the RSV season in Ireland typically runs from calendar week 40 (October) to calendar week 8 (February) of the following year, a patient who commences palivizumab early in the RSV season and continues to receive it for the duration of the RSV season is reported as a unique patient in two calendar years. This could lead to double counting if the yearly data are summed. Additionally, there is a lack of data regarding the month in which each patient received their first dose of palivizumab, meaning the uptake of palivizumab cannot be determined based on the available data.

Table 4.15 Numbers of claims for palivizumab, and unique patients to which the claims refer, made by community pharmacies in Ireland from 2019-2023, presented by age band and year

Year	0-4 years			<1 year			1 year			2 years			3-4 years		
	n	Claims	Claims per patient*	n	Claims	Claims per patient *	n	Claims	Claims per patient*	n	Claims	Claims per patient*	n	Claims	Claims per patient*
2019	768	1,875	2.4	292	731	2.5	408	979	2.4	60	150	2.5	8	15	1.9
2020	731	1,828	2.5	258	675	2.6	400	976	2.4	60	146	2.4	13	31	2.4
2021	627	1,466	2.3	225	538	2.4	334	763	2.3	63	152	2.4	5	13	2.6
2022	642	1,480	2.3	226	565	2.5	347	788	2.3	63	115	1.8	6	12	2.0
2023	637	1,522	2.4	243	602	2.5	309	728	2.4	82	186	2.3	3	6	2.0
Total	**3,405**	**8,171**	**2.4**	**1,244**	**3,111**	**2.5**	**1,798**	**4,234**	**2.4**	**328**	**749**	**2.3**	**35**	**77**	**2.2**

Note: 'Claims' refers to the number of unique prescriptions claimed for by community pharmacists from the Primary Care Reimbursement Service for each calendar year; n – number of unique patients.

* Average (mean) number of claims per patient calculated for all patients aged 0 to 4 years and for each age group separately.

Source: Primary Care Reimbursement Service.

In Ireland, the childhood immunisation programme is provided for free by the HSE.[215] Children aged 2 to 13 months receive vaccinations against the following diseases, across five GP visits: diphtheria, haemophilus influenza b, hepatitis B, measles, meningococcal B, meningococcal C, mumps, pertussis (whooping cough), pneumococcal disease, polio, rotavirus, rubella (German measles) and tetanus.[215] Quarterly immunisation uptake rate data on vaccinations provided within the childhood immunisation programme is provided by the HPSC. Data are available from Quarter 1 (Q1) 1999 up to Q3 of 2023.[216] For this analysis, data from 2018 to 2022 were only included, as this time period captured the first complete year of data collected following the most recent change to the national immunisation programme (the addition of the rotavirus and meningococcal B vaccines in late 2016)[217] up to the most recent data for a complete year (2022). Average annual immunisation uptake rates in infants aged 12 months are reported in Table 4.16. Considering all vaccines included in the schedule, uptake ranged from 87.2% to 90.0%.

Table 4.16 Average annual immunisation uptake rates (%) in infants aged 12 months in Ireland, for the period 2018 to 2022

	6-in-1$_3$*	MenB$_2$	MenC$_1$	PCV$_2$	Rota$_2$	All vaccines
Year	%	%	%	%	%	%
2018	89.2	92.3	89.3	89.0	89.0	89.5
2019	89.8	92.7	89.9	89.7	89.3	90.0
2020	87.9	92.1	87.9	87.8	89.4	88.5
2021	86.7	90.6	86.7	86.5	88.2	87.2
2022	87.0	90.8	87.0	86.8	88.1	87.5

Key: MenB$_2$: two doses of vaccine against meningococcal group B; MenC$_1$: one dose of vaccine against meningococcal group C; PCV$_2$: two doses of pneumococcal conjugate vaccine; Rota$_2$: two doses of vaccine against rotavirus before 8 months and 0 days.
*6-in-1$_3$: introduced to the immunisation programme in July 2008, the 6-in-1 is a single injection which provides one dose of vaccine for each of the following diseases: diphtheria, tetanus, pertussis, haemophilus influenzae type b, hepatitis B and polio. The 6-in-1 is provided on a three-dose schedule.
Source: Health Protection Surveillance Centre.[216]

Average annual immunisation uptake rates in children aged 24 months are reported in Table 4.17. For 2022, these data indicate an average immunisation uptake rate for all vaccines of 87.2% in children aged 24 months. Average annual immunisation uptake rate has declined slightly yearly since 2020 (2020: 89.4%, 2021: 88.6%, 2022: 87.2%).

Table 4.17 Average annual immunisation uptake rates (%) in children aged 24 months in Ireland, for 2018 to 2022

	6-in-1$_3$*	Hib$_b$	Hib$_4$	MenB$_3$	MenB$_{complete}$	MMR$_1$	MenC$_b$	MenC$_2$	PCV$_b$	PCV$_3$	Rota$_2$	All vaccines
Year	%	%	%	%	%	%	%	%	%	%	%	%
2018	94.5	89.7	N/A	N/A	N/A	92.4	87.9	87.4	91.5	89.9	N/A	90.5
2019	93.7	89.6	85.8	89.8	91.2	91.3	89.1	86.3	87.9	86.2	90.1	89.2
2020	94.2	89.5	85.9	90.5	92.0	91.8	88.9	85.9	88.2	86.5	90.3	89.4
2021	93.5	88.4	85.8	89.4	90.7	90.4	87.8	85.2	86.9	85.5	90.9	88.6
2022	92.7	86.5	83.1	88.5	90.8	89.5	86.0	82.8	85.2	83.8	90.5	87.2

Key: Hib$_b$: one booster dose of vaccine against haemophilus influenzae type b on or after 12 months of age; Hib$_4$: four doses of vaccine against haemophilus influenzae type b (with the first three doses given before 1st birthday and the 4th dose given on or after first birthday and before second birthday); MenB$_3$: three doses of vaccine against meningococcal group B (with the first two doses given before first birthday and the third dose given on or after first birthday and before second birthday); MenB$_{complete}$: those at 24 months of age who have received three doses of vaccine against meningococcal group B as defined above and those who have received two doses of MenB on or after 10 months of age and before second birthday with doses two months apart; MMR$_1$: one dose of MMR (measles, mumps and rubella) on or after first birthday (excludes MMR given before first birthday); MenC$_b$: one dose of vaccine against meningococcal group C on or after 12 months of age; MenC$_2$: two doses of vaccine against meningococcal group C (MenC$_2$ at 24 months from Q3 2017 is two doses of MenC with the first dose given before first birthday and the second dose given on or after first birthday and before second birthday); PCV$_b$: one dose of pneumococcal conjugate vaccine on or after 12 months of age; PCV$_3$: three doses of pneumococcal conjugate vaccine (since Q4 2018 defined as three doses of PCV with the first two doses given before first birthday and the third dose given on or after first birthday and before second birthday); Rota$_2$: two doses of vaccine against rotavirus before 8 months and 0 days; N/A: not applicable.

*6-in-1$_3$: introduced to the immunisation programme in July 2008, the 6-in-1 is a single injection which provides one dose of vaccine for each of the following diseases: diphtheria, tetanus, pertussis, haemophilus influenzae type b, hepatitis B and polio. The 6-in-1 is provided on a three-dose schedule.

Source: Health Protection Surveillance Centre.[216]

A COVID-19 vaccine is available free of charge for infants and children aged 6 months to 4 years, but is recommended only for those with conditions associated with higher risk of severe COVID-19 disease.[218] An interval of at least 14 days is recommended between administration of the COVID-19 vaccine and the administration of other vaccines. The HSE advises that for children aged under 4 years, vaccines included in the childhood immunisation programme should be prioritised over COVID-19 vaccination.[219] While the HPSC publish reports on COVID-19 vaccination uptake in Ireland periodically, disaggregated data for children aged 0 to 4 years is not provided.[220]

In 2021, a national survey of parents' views on childhood vaccinations was conducted in Ireland.[221] A total of 855 parents (of children aged 0 to 4 years) successfully completed the survey, with 96.1% of parents self-reporting uptake of the recommended vaccines. Trust in official vaccine information sources was reported as high (91.5%), and 89.2% of parents surveyed reported trust in the vaccine information provided by healthcare professionals and the HSE.[221] Within the same survey, parents were asked about the potential acceptability of a COVID-19 vaccine for their child or children,[222] as no COVID-19 vaccine was available to children aged 0 to 4 years in Ireland at the time the survey was conducted. Out of the 855 parents surveyed, 50.6% reported that they intended to vaccinate their child against COVID-19, while 28.7% reported that they did not intend to vaccinate their child, and 20.2% were unsure. The most frequently reported reasons noted by parents who reported that they would not vaccinate their child (n=245) were concerns that their child might have a serious side effect from the vaccine (45.6%), a need for further information (28.3%) or a belief that COVID-19 is not a serious illness in children (25.4%). Of those who reported that they did not intend to vaccinate their child or were unsure (n=422), the most frequently reported information needs related to side effects of the vaccine (64.7%) and vaccine safety (60.3%).

Antenatal immunisation

A number of vaccines are offered free of charge by the HSE to pregnant women, including the seasonal influenza vaccine, the pertussis (whooping cough) vaccine and the COVID-19 vaccine.

The seasonal influenza vaccine is available from October to the end of April each year, and can be administered to a pregnant woman at any point during the pregnancy.[223] It is recommended during pregnancy as influenza occurrence may lead to premature birth, lower birth weight, stillbirth and or hospitalisation.[223] WHO influenza vaccination coverage data indicates that 62% of pregnant women in Ireland received influenza vaccination in 2018, and this decreased to 42% in

2020.[224] Influenza vaccination uptake rates in further years are not reported by the WHO. These data are voluntarily reported annually through the WHO/UNICEF Joint Reporting Form on Immunization, which may contribute to the sporadic reporting.

The pertussis vaccine offered to pregnant women is most effective when administered between 16 and 36 weeks of pregnancy.[225] There are currently no national data regarding the uptake rate of the pertussis vaccine in pregnant women in Ireland.

The COVID-19 vaccine is recommended for pregnant adolescents or adults.[218] A single primary dose or a booster dose can be given at any time in pregnancy, but ideally between 20 and 34 weeks. The booster dose should be given at least six months after the last COVID-19 vaccine dose or SARS-CoV-2 infection. For those who are pregnant and are immunocompromised, a second booster dose within the same pregnancy may be considered if six months has elapsed since the last booster dose or infection. The HPSC publish reports on COVID-19 vaccination uptake in Ireland periodically.[226] A 2024 ECDC report on COVID-19 vaccination coverage during the 2023-2024 season reported that 19.6% of pregnant women in Ireland received a single dose of a COVID-19 vaccine between September 2023 and March 2024.[227] This estimate is based on data that were collected through TESSy, which the HPSC reports to, which are collected through the COVAX system.[228] COVAX is the HSE's vaccination platform software system application used to manage, monitor and support the process of administering the COVID-19, influenza and pneumococcal vaccinations across Ireland.[229] However, it is important to note that the total number of vaccinated pregnant women are only captured in the COVAX system in absolute numbers as opposed to rates of all pregnant women,[230] therefore some caution is advised with regards to the interpretation of the 19.6% estimate reported by the ECDC.

It is important to consider that the motivation for accepting a vaccine during pregnancy may differ depending on the aim of the vaccine offered.[231] For example, influenza and COVID-19 vaccines, when administered during pregnancy, are primarily aimed at protecting the mother.[231] However, similar to the maternal RSV vaccine, the primary aim of the pertussis vaccine during pregnancy is to provide passive immunity for the newborn baby, protecting them in the first few months of life.[232] While pregnant women can also become sick with whooping cough, the risk of severe infection and death is much greater in newborns.[233] The aim to protect the baby has been reported to be a strong motivation for vaccine uptake in pregnant women.[231]

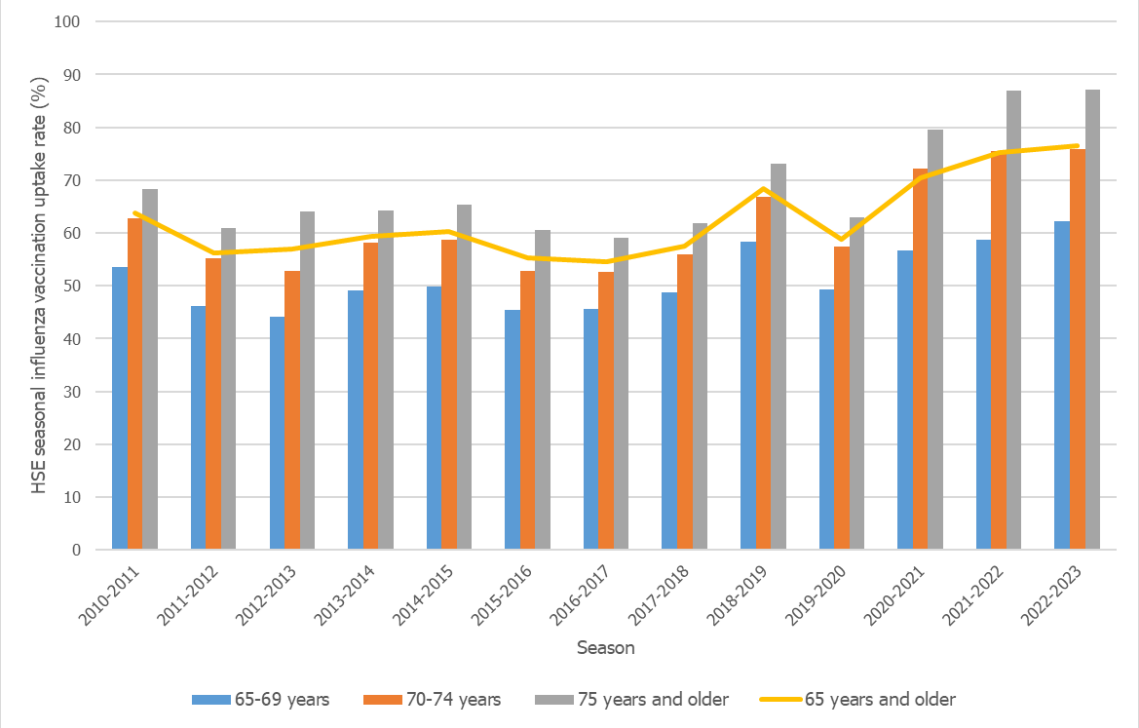
A 2023 scoping review aimed to understand the reasons for, and approaches to, non-uptake of pertussis and influenza vaccinations in pregnant women in the UK and

Ireland.[234] Themes identified were awareness and acceptability of vaccines, healthcare professional factors, organisational initiatives and awareness campaigns, information interpretation (including factors relating to ethnicity and socio-economic status), and pregnancy-related factors. Overall, the findings of the review highlighted that pregnant women need clear, comprehensible information, ideally provided by their healthcare professionals, in a way that is meaningful and addresses their circumstances and risk perceptions.

Older adults (aged 65 years and older)

In Ireland, a number of vaccines are offered free of charge by the HSE to adults aged 65 years and older, including the seasonal influenza vaccine, pneumococcal vaccine and the COVID-19 vaccine. Vaccination uptake rate data for the pneumococcal vaccine in Ireland is currently unavailable. The seasonal influenza vaccine is available from October to the end of April each year. Vaccination uptake rate data are provided by the HPSC and include data across settings including GP practices, community pharmacies, long-term care facilities (LTCFs) and hospitals. Figure 4.17 reports seasonal influenza vaccination uptake rate for adults aged 65 years and older, by age group and season, from the 2010-2011 season to the 2022-2023 season. Excluding the 2020-2021 and 2021-2022 seasons which were influenced by COVID-19, the average seasonal vaccination uptake rate for this period was 60.7% (range: 54.5% to 76.5%) in those aged 65 years and older. Uptake rates were highest in those aged 75 years and older. Across the seasons reported, the average vaccination uptake rates in those aged 65 to 69 years was 50.2% (range: 44.1% to 62.3%), 59.0% (range: 52.6% to 75.8%) in those aged 70 to 74 years, and 66.1% (range: 59.0% to 87.1%) in those aged 75 years and older. The 2022-2023 season was the first season in which the vaccination of healthcare workers and LTCF residents was included in these data, which may account for some of the reported increase in uptake in that season relative to prior seasons.[235]

Figure 4.17 Seasonal influenza vaccination uptake rate from 2010-2011 to 2022-2023 in those aged 65 years and older, reported by age group and season



Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional.
Source: Health Protection Surveillance Centre.

The primary COVID-19 vaccination programme for adults, including adults aged 65 years and older, commenced in December 2020. Booster doses were offered from November 2021. From April 2022, spring and autumn booster doses were offered to specific cohorts, including adults aged 65 years and older — that is, a second booster from April 2022, a third booster from October 2022, and fourth booster from April 2023.[236] From spring 2024, COVID-19 vaccination is recommended for adults aged 60 to 69 years who are immunocompromised, and for all adults aged 80 years and older. Vaccination is available to adults aged 70 to 79 years who request vaccination, following a discussion with their healthcare provider.[218]

COVID-19 vaccination uptake reports are published periodically by the HPSC.[220] These reports indicate that COVID-19 vaccination uptake rate was high among adults aged 65 years and older for the primary course and initial booster doses offered. As of June 2023,[236] COVID-19 vaccination uptake rates among adults aged 65 years and older was 99.4% for the primary course, 97.5% for the first booster course, 80.9% for the second booster course, and 55.5% for the third booster dose. Complete vaccination uptake data were not available for the period during which the fourth booster dose was offered. For the 2023-2024 COVID-19 autumn booster season (that is from September 2023 to February 2024), vaccination uptake rates

were 56.5% in adults aged 65 years and older, and 62.2% in adults aged 70 years and older.[230]

Barriers to seasonal influenza vaccine uptake that have been identified in older adults include perceived low risk of illness, perceived inconvenience and financial burden associated with vaccination, lack of knowledge and or information on influenza and influenza vaccines, and concerns relating to vaccine effectiveness and safety. Factors positively associated with influenza vaccine uptake include greater perceived threat from influenza, perceived effectiveness of the vaccine, and receiving information and or recommendations from healthcare professionals, family or friends.[237, 238]

In terms of COVID-19 vaccination acceptance, hesitancy and resistance, a 2021 survey included nationally representative samples of the adults populations in Ireland (n=1,041) and the UK (n=2,025).[239] Overall, 65% (95% CI: 62.0 to 67.9) of Irish respondents were accepting of a COVID-19 vaccine, 26% (95% CI: 22.9 to 28.3) were hesitant, and 9% (95% CI: 7.7 to 11.3) were resistant to a COVID-19 vaccine. Findings were not reported separately for the 12.2% (n=127) of Irish respondents aged 65 years and older. However, in both the Irish and UK samples, younger adults were among the groups most likely to be vaccine-resistant or hesitant. In the overall Irish sample, combined vaccine-hesitant and resistant respondents reported lower levels of trust in scientists, healthcare professionals, and the state compared with those accepting of the vaccine.

A 2024 scoping review aimed to understand the positive and negative impacts of the COVID-19 pandemic on adult vaccination programmes in general.[240] Positive developments identified included unprecedented funding, international cooperation, technical and process innovation, investments in infrastructure and health workforce, and improved health literacy in relation to vaccines. Inequitable vaccine access and affordability were identified as specific barriers to vaccination uptake in older adults, as well as underrepresentation of older adults in clinical trials.[240]

4.6.3 Immunisation uptake rates in EU/EEA countries and the UK

Children (aged 0 to 4 years)

Rates of uptake and adherence to palivizumab prophylaxis among eligible children are not routinely reported across EU/EEA countries or the UK. Available data from a variety of international literature suggests that palivizumab uptake and adherence rates vary considerably among eligible cohorts. A 2008 systematic review reported palivizumab adherence rates among eligible children ranging from 25% to 100%, based on 25 included studies from both the US and Italy.[241] A study using data from the Canadian registry of palivizumab reported that 60.9% (n=11,710/19,235)

of enrolled children received the appropriate number of doses of palivizumab at the appropriate intervals across nine RSV seasons, from October 2005 to May 2014.[242] A cohort study in the Netherlands reported that 71.8% (n=135/188) of eligible preterm infants born during the two-year study period (2015-2017) received palivizumab. The authors noted that further research including parents and clinicians would be required to explore the reasons for non-uptake.[243]

Preliminary nirsevimab uptake data are available for Luxembourg and Spain, where programmes for universal immunisation of infants against RSV were introduced during the 2023-2024 RSV season. From the commencement of the programme in Luxembourg in October 2023 to mid-December 2023, the estimated average neonatal coverage was 84% (range: 66% to 94% between maternity wards). Coverage for infants immunised in outpatient settings was not monitored due to the lack of a national immunisation registry.[80] In Spain, nirsevimab was introduced and offered to infants as part of the national immunisation programme from late September 2023. Based on preliminary data from 14 Autonomous Communities covering the period up to mid-February 2024, the average neonatal coverage was 91.9% (range: 85.7% to 96.7%). Coverage was lower in infants born outside of the RSV season (between 1 April 2023 and the start of the RSV season), with an average coverage rate of 87.3% (range: 44.7% to 97.0%).[122]

A national programme for the immunisation of infants with nirsevimab was also commenced in France in September 2023. As uptake rates were expected to be high, nirsevimab was preferentially allocated to newborns in maternity wards prior to discharge and to infants aged less than one month in hospital wards. Uptake data for this programme are not yet available. However, preliminary data indicated that by 26 December 2023, 237,000 doses of nirsevimab were distributed nationally.[244]

Parental attitudes towards immunisation of infants against RSV provide indications of potential immunisation uptake rates. A survey commissioned by the National Institute of Public Health and the Environment (RIVM) in the Netherlands asked parents of young children (that is, children aged less than 3.5 years) their intentions regarding potential immunisation against RSV at two time points, in 2013 and in 2022. In 2013, approximately 45-50% of respondents (n=800) agreed that they would immunise their child against RSV, if immunisation were available. In 2022, just over 60% of respondents (n=1,000) agreed. In both years, approximately 5% of respondents stated that they would not avail of immunisation against RSV for their child.[245]

A 2021 survey conducted in China, France, Germany, Italy, Japan, Spain, the UK, and the US asked individuals who were expecting their first baby or parents of children aged less than 2 years about their knowledge of RSV and attitudes towards

immunisation. The study was funded by the marketing authorisation holder for nirsevimab. Knowledge of RSV was limited among respondents in European countries (France, Germany, Italy, Spain, the UK), with 44% (n=1,673/3,801) reporting that they had never heard of RSV (range: 37% in Spain to 50% in France). When asked how likely they would be to accept immunisation against RSV, if recommended as part of the immunisation programme and by their child's healthcare professional, 59% of respondents in European countries stated that there was a high chance they would accept (range: 43% in France to 71% in Spain). Respondents stated that the most important information they would like to have about RSV immunisation related to its safety, and secondly, its efficacy.[246]

Antenatal

RSVpreF (Abrysvo®) is authorised in Europe for immunisation of pregnant women to help protect their infants from lower respiratory tract disease caused by RSV (for the first six months of the infant's life).[9] As yet, no country in the EU/EEA or UK has implemented RSVpreF (Abrysvo®) as part of a national immunisation programme, and therefore no vaccination uptake rate data for RSVpreF (Abrysvo®) is available. However, similar to Ireland, a number of EU/EEA countries and the UK provide antenatal vaccines free of charge to pregnant women, including the seasonal influenza vaccine, the pertussis (whooping cough) vaccine and the COVID-19 vaccine.[247]

Twenty-nine EU/EEA countries have national recommendations for seasonal influenza vaccination during pregnancy.[248] Within a 2023 ECDC technical report, four of these countries reported influenza vaccination coverage rates in pregnant women — Hungary, Lithuania, Slovenia and Spain — with rates ranging from 1.7% to 61.9% for the 2020-2021 season.[248] Further seasonal influenza vaccine uptake data in pregnant women was also identified for Spain[249] and the UK.[250] In Spain, the seasonal influenza vaccine is recommended during any trimester. Vaccination uptake rates of 29.6%, 40.6%, 50.0%, 62.3%, 55.3%, 53.6% and 57.8% have been reported for 2017, 2018, 2019, 2020, 2021, 2022 and 2023 respectively.[249] In the UK, the seasonal influenza vaccine is recommended in the autumn, but can be administered anytime during pregnancy.[251] The uptake rate has declined by 13% in an eight-year period between 2016-2017 (44.8%)[252] and 2023-2024 (31.8%).[253] However, it should be noted that the coverage period for which seasonal influenza vaccination uptake rates are reported has changed from September to January (2016-2017 and 2017-2018), to September to February (2018-2019 to 2022-2023), to annual coverage for 2022-2023 and 2023-2024 (in the 2022-2023 period, both September to February and annual coverage uptake rates were reported).

Pertussis vaccination uptake rate data was also identified for Spain[249], the Netherlands[254] and the UK.[255] In Spain, the pertussis vaccine is recommended, preferably between weeks 27 and 32 of gestation, but can also be offered from 20 weeks gestation if there is a risk of preterm delivery.[256] Increasing annual vaccination uptake rates have been reported yearly in Spain since 2017, with rates of 80.0%, 80.1%, 83.6%, 85.2%, 87.0%, 87.2% and 88.5% reported for 2017, 2018, 2019, 2020, 2021, 2022 and 2023 respectively.[249] In the Netherlands, the pertussis vaccine is recommended at 22 weeks gestation and an estimated uptake rate of 70% was reported for the year 2020.[254] In the UK, the pertussis vaccine is recommended from 26 weeks to 32 weeks of gestation, but can also be administered up until labour.[257] The annual pertussis vaccination uptake rate in pregnant women in the UK has declined by almost 10% in a four-year period between 2019 and 2023, with rates of 70.5%, 67.8%, 64.7% and 60.7% reported for 2019-2020, 2020-2021, 2021-2022 and 2022-2023.[255]

It should be noted that in the literature, both Spain and the UK are identified as having high-performing vaccination programmes (high vaccination coverage rates) for influenza and pertussis vaccination in pregnant women.[258] Key components associated with these high-performing vaccination programmes included the mobilisation of health authorities, prenatal healthcare professionals and the provision of educational material to these healthcare professionals.[258]

There is limited information available with regards to COVID-19 vaccination uptake rates in pregnant women in the EU/EEA and the UK. A 2024 ECDC report on COVID-19 vaccination coverage during the 2023-2024 season reported that 7.8% of pregnant women in Spain received a single dose of a COVID-19 vaccine between September 2023 and March 2024.[227] In the UK, 0.5% of women who gave birth in September 2022 had received a single dose of the COVID-19 vaccine, prior to delivery, in the autumn period. This then increased to 18.1% of women who gave birth in January 2023 and peaked at 19% of women who gave birth in February 2023.[259]

Older adults (aged 65 years and older)

RSV vaccination uptake data was not identified for older adults in EU/EEA countries and the UK. As outlined in Chapter 3, of the 31 EU/EEA countries and the UK, only the UK were identified as planning to implement a publicly-funded programme offering once-off RSV vaccination for all adults aged 75 to 79 years from September 2024.[103] In addition, in the Czech Republic, RSV vaccines are available on an individual basis for adults aged 65 years or older and are partially funded through insurance.[137, 138]

The ECDC have published reports on seasonal influenza immunisation policies and vaccination coverage in EU/EEA countries. These reports aim to monitor compliance with the 2009 Council recommendation for EU Member States to achieve a vaccination coverage rate of 75% in certain target groups, including older adults.[260] The most recent report described trends in coverage rates for the 2018–2019 to 2020–2021 influenza seasons.[248] In 2020-2021, the median coverage rate was 59% (range: 4.5% (Latvia) to 75% (Denmark)) compared with a median coverage rate of 51% during the 2018-2019 season (range: 8.1 (Latvia) to 68.5% (Ireland)). In all but two countries (Latvia and Slovakia), vaccination coverage rates increased during the 2020-2021 season compared with the previous two seasons. However, Denmark was the only country that met the target coverage of 75% during the 2020-2021 season. A previous report described coverage rates for the 2016-2017 and 2015-2016 influenza seasons.[261] Vaccination coverage rates varied from 2.0% in Estonia to 72.8% in the UK (median 47.1%) in 2016-2017. The highest vaccination coverage rates were reported by the UK, which almost achieved the EU target of 75% in those aged 65 years and older.[261] For both reports, Member States' vaccination recommendations varied, as did their definitions of older adult age groups. Overall, most countries considered older adults to be those aged ≥65 years, but some countries included those aged ≥50, ≥55, ≥59 or ≥60 years. Given that seasonal influenza vaccination uptake increases with age, countries adopting a lower definition for older age may be likely to report lower uptake.

The UK Health Security Agency (UKHSA) and, prior to 2022, Public Health England have published annual reports on seasonal influenza vaccination uptake among all patients registered with a GP in England. For the 2022-2023 season, uptake was 79.9% in those aged 65 years and older.[262] The highest vaccination uptake ever recorded in England for this age group was achieved in 2021-2022, with an uptake rate of 82.3%, compared with 80.9% in the 2020-2021 season,[263] 72.4% in 2019-2020 season and 72.0% in 2018-2019 season.[264] This echoes the trend observed in EU/EEA countries of increased seasonal influenza vaccination uptake since the onset of the COVID-19 pandemic.

The ECDC published an interim report on COVID-19 vaccination coverage in 24 of 30 EU/EEA countries. In that report, vaccination coverage was defined as the percentage of the target population who received one dose of the COVID-19 vaccine during the reporting period — that is, between 1 September 2023 and January 2024. Disaggregated data was reported for adults aged 60 years and older and those aged 80 years and older.[227] For those aged 60 years and older, median coverage during the reporting period was 11.1% (range: 0.01 to 65.8). Of the 24 countries reporting data for adults aged 60 years and older, none reported a coverage rate greater than or equal to 80%. For those aged 80 years and older, median coverage was 16.3%

(range: 0.01 to 88.2). Of the 24 countries reporting data for this target group, one country reported a coverage rate greater than or equal to 80% (Denmark: 88.2%). However, as an interim report, data completeness varied considerably across countries. In addition, coverage rates for those aged 60 years and older should be interpreted with caution, as the COVID-19 vaccine is only recommended for those aged 65 years and older in a number of the included countries.

4.7 Economic burden of respiratory syncytial virus

Respiratory syncytial virus places a large economic burden on society and healthcare systems internationally.[265, 266] In considering the economic burden associated with RSV, in both children aged 0 to 4 years and adults aged 65 years and older, both direct and indirect costs are relevant.[54, 265] Direct costs include those related to providing care for the patient — for example, primary care visits, medication costs and hospitalisation costs.[54, 266-268] Indirect costs include productivity losses (caregiver for children aged 0 to 4 years,[269] caregiver and or patient for adults aged 65 years and older[54]), due to RSV-associated illness or death. Management of RSV is often achieved through primary care. The cost to patients of accessing primary care varies substantially across countries and will impact on the applicability of the findings to the Irish setting. Additionally, estimating the burden of RSV in secondary care is often a challenge due to diagnostic uncertainty. For example, the symptoms of RSV are non-specific and not all patients will have specimens collected and tested. Moreover, some patients may acquire RSV during their inpatient stay rather than RSV being the cause of admission, although this is partly accounted for using the primary diagnosis code.

Within the context of this rapid HTA, a brief overview of relevant literature in children aged 0 to 4 years and adults aged 65 years and older was undertaken.

Children (aged 0 to 4 years)

The findings reported in this chapter are consistent with those reported in an Irish study, published in 2023, which estimated the economic burden of RSV-related hospitalisations based on data sourced from HIPE. The study highlighted the substantial burden particularly in those aged less than two years (estimated at €7.4 million for 2021). However, they considered that this may an underestimate due to the under-reporting of RSV. They suggested that if hospitalisations due to acute bronchiolitis were also considered attributable to RSV, the estimated burden for 2021 would have exceeded €10 million for this age group.[270]

A 2023 RESCEU study investigated the economic burden of RSV in infants, in four European countries.[269] Data related to RSV symptoms and diagnosis were prospectively collected for healthy-term infants, recruited at birth, throughout their

first year of life. Parents or caregivers were also asked to report healthcare resource use and work absenteeism related to infant RSV occurrence. Mean healthcare costs for infants requiring hospitalisation for RSV were estimated at €4,588 (95% CI: €3,085 to €6,229) per RSV episode.[269] This cost was over 20 times higher than for infants requiring ambulatory care only (€168, 95% CI: €130 to €203). Mean cost per RSV episode increased when caregiver productivity losses were included for both infants requiring hospitalisation (€5,095, 95% CI: €3,507 to €6,894) and infants requiring ambulatory care only (€255, 95% CI: €198 to €318).[269]

A 2022 industry-sponsored UK study investigated the economic burden of RSV in children less than five years.[271] Data extracted from published literature were extrapolated to the UK population in 2019. The mean total cost per child aged less than five years, presenting to the National Health Service with RSV, was estimated at £97. The annual healthcare costs and productivity losses resulting from RSV in children aged less than five years was estimated at approximately £80 million, with almost 80% of this cost attributable to direct healthcare costs, such as hospital admissions and outpatient attendances.[271] An estimated £14 million was attributable to productivity losses and £1.5 million to carers' out-of-pocket expenses.[271]

Older adults (aged 65 years and older)

A Canadian study carried out in 2022 explored RSV healthcare costs across age bands, including adults aged 65 years and older.[272] Data related to laboratory-confirmed RSV cases and RSV-Acute Respiratory Infection (ARI) identified via ICD-10 codes, from 2010 to 2019, were sourced from administrative healthcare databases in Alberta. Each case was matched to non-RSV controls drawn from Alberta's publicly-funded health insurance plan. Adults aged 65 years and older represented 13.5% and 9.1% of total RSV and RSV-ARI cases identified, respectively. Older adults have some of the highest costs associated with RSV disease, both for laboratory-confirmed RSV cases and RSV-ARI. Additionally, higher median costs were estimated for laboratory-confirmed cases of RSV at 30 (Canadian Dollars ($CAD) 3,964) and 365 ($CAD 37,842) days following diagnosis, in adults aged 65 to 79 years, compared with matched controls (30 days: $CAD 45; 365 days: $CAD 1,840).[272] Attributable costs for both laboratory-confirmed RSV cases and RSV-ARI, at 30 and 365 days, were driven by inpatient costs.[272]

A 2023 study carried out in Germany estimated the direct medical costs of RSV hospitalisation.[197] RSV hospitalisation data, including costs, were sourced from the German Federal Statistical Office database on German Hospital Statistics, for the period 2010 to 2019. While disaggregated data were not provided for adults aged 65 years and older, a subgroup of older adults (aged 60 years and older) was outlined,

with a median age of 79 years (IQR: 72 to 85 years). Adults aged 18 to 59 years had the highest mean per patient direct hospitalisation cost at €7,215 (standard deviation (SD) ± €13,564), followed by older adults at €5,731 (± €10,338).[197] When further disaggregated by age however, the highest mean was identified for those aged 60 to 69 years (€ 8,442 ± €18,404). When compared with the other nine age bands included within this analysis (ranging from age less than 10 years to 90 years and older), a higher proportion of patients presenting with immune disorders, having complications such as sepsis and bacterial pneumonia, and receiving treatment such as intensive care and extracorporeal membrane oxygenation treatment were in this subgroup of adults aged 60 to 69 years, which may have contributed to the higher hospitalisation costs.[197]

A 2022 RESCEU study investigated the economic burden of laboratory-confirmed RSV and influenza in older adults not requiring hospitalisation in three European countries.[54] While disaggregated data were not provided for adults aged 65 years and older, the median age for RSV and influenza groups was 75.1 years (IQR: 70.0 to 79.3) and 72.3 years (IQR: 66.5 to 78.0), respectively. From a healthcare payer perspective (patient plus healthcare provider costs), mean and median direct costs per influenza episode (€42.5, median: 36.0 [IQR: 3.3 to 66.7]), were comparable, albeit slightly higher, than direct costs per RSV episode (€26.37, median: 5.54 [IQR: 0 to 47.31]). The authors suggested that direct costs associated with influenza infection may be used as a proxy for RSV infection in older adults who do not require hospitalisation.

The findings reported in this chapter relating to the burden of RSV in older adults are also broadly consistent with those reported in an Irish study, published in 2023, which estimated the economic burden of RSV-related hospitalisations based on data sourced from HIPE.[270] They estimated that the cost of RSV-related hospitalisations for adults aged 65 years and older for the period 2017 to 2021 ranged from €147,000 in 2017 to €870,000 in 2019. However, if it was assumed that there is under-ascertainment of RSV, and that approximately 6.8% of hospitalisations in older adults for respiratory-related infections are due to RSV, they estimated that total hospitalisation costs due to RSV in those aged 65 years and older exceeded €8.1 million (€0.4 million and €7.7 million in reported and unreported RSV hospitalisation costs) in 2021.

4.8 Discussion

This chapter describes the epidemiology of RSV in Ireland, and the burden of disease in Ireland, EU/EEA countries and the UK among children aged 0 to 4 years, and adults aged 65 years and older. In summary, RSV surveillance data for Ireland show that, excluding 2020, there has been variability in the burden associated with

RSV in those aged 0 to 4 years and in adults aged 65 years and older, over the 10-year period since 2013. Specifically, in those aged 0 to 4 years, there has been year-to-year variation in the rate of notified RSV cases (range: 335.1 to 1,699.6 per 100,000), notified RSV ED visits (range: 34.0 to 785.0 per 100,000) and RSV-related hospital admissions (range: 190.3 to 790.1 per 100,000). This has also been observed in adults aged 65 years and older with year-to-year variation in the rate of notified RSV cases (range: 6.4 to 203.9 per 100,000), notified RSV ED visits (range: 9.5 to 58.7 per 100,000) and RSV-related hospital admissions (range: 1.3 to 74.6 per 100,000). It is noted that these data are reported by calendar year rather than by RSV season, so may not accurately reflect differences in disease severity and healthcare burden from one RSV season to the next.

When disaggregated by one- or two-year age bands, it was observed that those aged 0 to 4 years are not homogenous. The burden of RSV is greater in infants aged less than one year compared with those aged 1 to 4. For example, rates of notified RSV cases, RSV-related hospital admissions and RSV ED visits were highest in infants aged less than one year, when compared with infants aged two to three years, and three to four years. An increased burden of RSV for infants aged less than one year is supported throughout the literature, with GBD 2019 data indicating that, while 33 million RSV-associated ALRI cases occurred globally in children aged five years or less in 2019, one in five of these cases occurred in infants aged 0 to 6 months.[53] A lack of previous exposure to RSV, and therefore lack of partial immunity, may contribute to the increased RSV incidence in those aged less than one year.[268] This may be of further concern as evidence suggests an association of infant RSV occurrence with further respiratory conditions, such as asthma, in later life.[273, 274] The Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure (INSPIRE) study included 1,741 infants with available data to assess RSV infection status in the first year of life. This study outlined that infants not infected with RSV during their first year of life have a substantially reduced risk of developing childhood asthma (adjusted Risk Ratio: 0.74 [95% CI: 0.58 to 0.94], p=0.014), compared with infants with a RSV infection in their first year.[29] Additionally, the authors estimated that 15% of the five-year current asthma cases identified within their study could be prevented by avoiding RSV infection during infancy. It is suggested that interventions that prevent, delay, or decrease the severity of the initial RSV infection should be studied as a strategy to potentially reduce the prevalence of childhood asthma at the population level.[29]

The population aged 65 years and older are also not homogenous. When data for this group are disaggregated by five-year age band, in general, the burden of RSV increased with age. Adults aged 80 years and older accounted for on average 46% (range: 35% to 48%) of notified cases, 43% (range: 40% to 46%) of RSV-related

ED visits and 46% (range: 29% to 50%) of RSV-related hospital admissions, with the highest rates typically observed in those aged 85 years and older. Compared to the amount of literature available around the burden of RSV in children, there is currently limited literature available around the burden of RSV in older adults,[275] and in particular adults aged 80 years and older. However, a 2023 analysis of RSV-associated hospitalisation estimates in six EU countries between 2006 and 2017 outlined that when data was extrapolated to 28 EU countries (including the UK), adults aged 85 years and older displayed the highest estimated rate of annual RSV-associated hospitalisations when compared to the remaining adult age bands (18- to 64-year-olds, 65- to 74-year-olds and 75- to 84-year-olds).[200] Furthermore, the authors also estimated that 39% of the annual number of RSV-associated hospitalisations in the EU during this period occurred in adults aged 65 years and older.[200] A 2022 systematic review on the burden of RSV in older adults in high-income countries outlined that the presence of comorbidities, such as chronic obstructive pulmonary disease and asthma, increased the risk of RSV-related hospitalisation of those aged 60 years and older.[276] Additionally, a 2018 prospective study of adults 60 years and older seeking care for acute respiratory illness, also reported that the relative risk of a serious outcome (such as hospital admission) was increased in adults with RSV aged 75 years and older, compared with their younger counterparts (60- to 64-year-olds).[277] Aside from the burden of RSV-related respiratory disease, adults hospitalised with RSV may also be at greater risk of experiencing acute cardiac events and subsequent severe outcomes. A cross-sectional study conducted over five RSV seasons found that just over 1 in 5 hospitalised older adults with laboratory-confirmed RSV infection experienced a cardiac event (weighted estimated prevalence 22.4%; 95% CI: 21.0 to 23.7).[278] Those who experienced an acute cardiac event had a greater risk of severe outcomes compared with those who did not have an acute cardiac event (weighted estimated prevalence of ICU admission 25.8% vs 16.5%; adjusted risk ratio (ARR) 1.54; 95% CI: 1.23 to 1.93) and in-hospital death (8.1% vs 4.0%; ARR 1.77; 95% CI: 1.36 to 2.31).

It should also be noted that infants aged less than one year displayed the greatest burden of RSV, when compared with all of the age bands investigated, including disaggregated age bands in adults aged 65 years and older. Quarterly data for RSV hospital discharges outlined that the greatest proportion of discharges annually, in those aged 0 to 4 years, occurred in quarter four (October to December). When disaggregated further, these data outlined that the majority of quarter four hospital discharges occurred in infants aged less than one year. Internationally, RSV-related hospitalisations have displayed seasonality, with peak hospital admissions traditionally occurring in the winter for temperate countries,[279, 280] such as Ireland. A 2024 analysis of RSV surveillance data in seven countries outlined that, at the

beginning of an annual RSV epidemic, a larger proportion of RSV cases are made up of children aged one to four years compared with infants aged less than one year, and compared with those aged five years or older.[281] The authors proposed that this is likely due to RSV infection occurring in early childcare and education settings. However, as the RSV epidemic progresses, RSV cases become more likely to occur in infants aged less than one year, and those aged five years and older.[281] Given the heightened risk of hospital admission in infants aged less than one year infected with RSV,[282] and the RSV season typically starting in Ireland in October,[22] this may align with increased RSV hospital discharges in the last quarter of the year. This will likely have a significant seasonal knock-on effect on the healthcare system in terms of the healthcare utilisation associated with RSV, and other respiratory conditions such as influenza and pneumonia, which also experience increased healthcare utilisation in the winter season in Ireland.[283] This burden may be further increased in infants presenting with complex cases, such as those with RSV and a bacterial or viral co-infection. A 2023 prospective study of 433 RSV-positive infants aged less than one year outlined that nearly one in four infants were infected with at least one additional respiratory virus.[284] These infants displayed an increased need for ICU and mechanical ventilation, compared with infants without co-infection.[284] This is supported within the Irish Paediatric Critical Care Audit National Report 2021-2022 which outlined an annual peak in the number of respiratory admissions to both paediatric critical care units (PCCU) in Ireland (Children's Health Ireland at Crumlin and Temple Street), during quarter four of 2021 and 2022, respectively.[285] This report also outlined that PCCU bed occupancy reached or exceeded 100%, in both November and December of 2021 and 2022, further detailing the level of healthcare utilisation occurring in quarter four annually.[285] The burden on PCCUs observed during the peak of the RSV season may result in longer waiting times for children with less serious illnesses.[286] Maximal occupancy within the PCCU may also lead to the deferral of elective and routine inpatient procedures with potentially substantial clinical and economic impacts.[287]

In general, there is a trend of increased incidence of notified RSV cases and RSV-related hospital admissions over time. While the proportion of the Irish population aged 0 to 4 years has decreased slightly over time, from 7.8% in 2011 to 5.7% in 2022,[170] the proportion of the population aged 65 years and older has increased over the same period (11.7% in 2011[288] to 15.1% in 2022[289]). This proportion is set to continue to increase, with population projections predicting that the proportion of the total population aged 65 years and older in Ireland will reach 17.3% in 2028 and 19.0% in 2033.[290] Moreover, the population group aged 80 years and older (who, in this assessment, accounted for approximately 48% of hospital discharges in adults aged 65 years and older with a primary diagnosis of RSV) is set to rise even more dramatically, with projections estimating an almost

four-fold increase in the number of individuals aged 80 years and older (from 147,800 in 2016 to 549,000 in 2051) within the next 30 years.[291] This will significantly challenge the Irish healthcare systems as it aims to manage this increase in older people presenting with complex combinations of chronic conditions, geriatric conditions and disabilities, along with acute health events.[292]

It is unclear whether the increased incidence of notified cases is because incidence of RSV is genuinely higher due to greater transmission (through, for example, more mixing) or less immunity (for example, due to a more frail older adult population), or if it is due to increased testing for RSV. If the incidence of RSV is genuinely increasing over time, it would be important to understand the underlying causal factors, as this should inform the policy response. It is noted that there was an abrupt decline in RSV notifications between March 2020 (at the start of the COVID-19 pandemic) and September 2021.[293] This was most likely due to the implementation of non-pharmaceutical interventions (including the closure of childcare facilities and schools) to limit the transmission of SARS-CoV-2 which also limited the transmission of other respiratory pathogens. The COVID-19 pandemic also changed the landscape of respiratory virus testing in Ireland, with more laboratories conducting respiratory virus testing and the increased use of multiplex PCR assays to test for respiratory viruses, including RSV. A recent national laboratory survey of respiratory virus testing in acute hospital settings undertaken by the HPSC in July 2023 found that 93% of laboratories have on-site multiplex reverse transcriptase-PCR (RT-PCR) testing capacity for specimens from hospital inpatients and ICU patients with 83% testing for SARS-CoV-2, influenza and RSV, and 10% testing for SARS-CoV-2 and influenza.[294] This represents an almost three-fold increase in testing capacity compared with results of the previous survey conducted in 2016 (unpublished data). Two (7%) laboratories reported plans to introduce multiplex RT-PCR testing during the 2023-2024 winter season. In addition to RT-PCR testing, 33% of responding laboratories reported using rapid molecular methods in their laboratories for testing for SARS-CoV-2, influenza, and RSV.[294] The authors concluded that this decision to extend testing capacity was almost certainly driven by the COVID-19 pandemic. This recent expansion of testing will likely have contributed to the increase in the number of RSV notifications reported to the HPSC.

Assuming that the increase in capacity was driven by an increase in demand for testing, the trend of increasing incidence may be an artefact of increased surveillance and testing. If this is the case, then the most recent data are likely a more accurate reflection of the true burden of RSV on the healthcare system. It is acknowledged however that the most recent data still underestimate the true burden, as not all cases are (or will likely ever be) notified. Of note, 37% of hospital laboratories in the 2023 HPSC survey also reported testing specimens from nursing

homes and residential care facilities, while 30% reported testing specimens submitted from primary care practices. Given the lower access to testing capacity for those in primary care, the burden of respiratory viruses, including RSV, is likely underestimated in primary care.[294] While noting this, it is recognised that respiratory virus surveillance in residential care settings has increased and may have contributed to the increased detection of RSV in older adults in recent years. Rapid detection of respiratory pathogens in long-term care facilities is critical when implementing a comprehensive infection control plan.[295] Per the HPSC Winter 2023-2024 testing guidance,[296] it is recommended that any resident of a long-term care facility presenting with respiratory symptoms, or other symptoms compatible with COVID-19 or influenza, should undergo multiplex PCR testing for COVID-19 and influenza. Further testing for respiratory viruses may also be advised. In terms of children, however, expert opinion has reported that, in hospital emergency departments, testing for RSV in paediatric populations is very rare, and would only occur if the child was going to be admitted to hospital. Reports of limited RSV testing in primary care is supported by the sentinel and non-sentinel GP data reported as part of this assessment. From 2013 to 2023 (excluding the year 2020), for those aged 0 to 4 years, of all RSV-positive specimens notified through the CIDR system, on average, 6% came through sentinel GP practices and 29% came through non-sentinel GP practices per annum. In those aged 65 years and older, on average, 2% and 23% of RSV-positive specimens notified through the CIDR system came through sentinel and non-sentinel GP practices per annum, respectively. Expert opinion from the EAG has also highlighted that given the often atypical presentation of RSV symptoms in older adults, this cohort may be less likely to be tested. As such, the true burden of RSV in primary care is likely much higher than that reported.

International data on the burden of RSV-related disease in infants published by the RESCEU consortium substantiate the findings relating to the burden of RSV in this cohort in Ireland. A systematic analysis estimated the burden of ALRI due to RSV in children aged less than five years, and reported a disproportionately high burden of RSV-related morbidity and mortality in infants aged 0 to 6 months, and a smaller but still substantial burden in infants aged 6 to 12 months.[53] A systematic review and meta-analysis further explored the burden of, and risk factors for, RSV-related ALRI in children aged less than two years who were born prematurely. Overall, preterm infants accounted for 25% (95% Uncertainty Ratio: 16 to 37) of RSV-related ALRI hospitalisations in infants of any gestational age. Underlying medical conditions were the main factors associated with severe outcomes from infection, including congenital heart disease, tracheostomy, bronchopulmonary dysplasia, chronic lung disease, or Down syndrome (odds ratios ranging from 1.40 to 4.23).[297]

It should be noted that there is currently a lack of data surrounding the wider burden of RSV in Ireland. However, it was noted within the literature that parent and carer HR-QoL is substantially impacted by RSV-related hospitalisation of their child;[203] this included stress and worry related to the hospitalisation of their child. Furthermore, parents experienced negative impacts to their employment, such as a decrease in job productivity.[203] This impact of RSV-related hospitalisation of a child also extended beyond that of the child affected and their parent, with family cohesion and adaptability (or flexibility) negatively impacted.[204] In older adults, while there is limited literature available regarding the wider burden of RSV, this virus has been reported to negatively impact the daily activities and or productivity, social activities, relationships and employment of the person infected, during the acute infection period.[209]

The substantial burden associated with RSV in children aged 0 to 4 years and adults aged 65 years and older in Ireland is in the context of limited options for immunisation against RSV (specifically, the only available option being palivizumab for children at high risk of severe RSV-related disease). The impact on this burden of new technologies for active and passive immunisation of infants and older adults against RSV, which have recently been authorised in Europe, remains to be seen. As outlined in Chapter 3, a number of countries across the EU/EEA and the UK have developed or are developing national recommendations for immunisation against RSV in these cohorts based on evidence of the safety, efficacy and clinical effectiveness of these technologies. As immunisation strategies are implemented and monitored, further evidence of the clinical effectiveness of these technologies is expected to emerge. In addition to effectiveness, immunisation coverage rates influence the level of protection provided. Immunisation in Ireland is voluntary and is typically offered systematically to specific groups (for example, based on age and or risk of severe disease). Such programmes therefore rely on individuals knowing that immunisations are available, seeking and accessing immunisation, and being encouraged to avail of them.

For children, vaccinations recommended as part of the HSE's Primary Childhood Immunisation Schedule are available free of charge and can be administered over five GP visits from the ages of two months to 13 months. The HSE provides information for parents and or guardians to outline the contents of the programme and to address common questions or concerns.[298] As outlined in section 4.6, vaccination uptake among children in Ireland declined each year from 2020 to 2022. When considered in relation to the WHO's Immunization Agenda 2030 targets for vaccination coverage,[299, 300] uptake rates from 2018 to 2022 in Ireland have consistently been greater than 90% for children aged 24 months for diphtheria-tetanus-pertussis vaccination, delivered as part of the 6-in-1 vaccine. However,

pneumococcal conjugate vaccination uptake rates have consistently been below 90% for children aged 24 months over the same time period, and have declined from 89.9% in 2018 to 83.8% in 2022 (see Table 4.17). The WHO uses measles vaccination as a 'tracer' to identify the strength of immunisation programmes and as an identifier of age groups or communities who may be un-immunised or under-immunised.[299] In Ireland, uptake rates in children for the first dose of the MMR (measles, mumps and rubella) vaccine declined from 92.4% in 2018 to 89.5% in 2022. However, this excludes infants who received an MMR vaccine dose before their first birthday, so may be an underestimation of the total proportion of infants vaccinated.

Since the HSE's Primary Childhood Immunisation Schedule commences at the age of two months, the potential acceptance and uptake of immunisation for infants aged less than two months in Ireland is unknown. Historically, Bacillus Calmette-Guérin (BCG) vaccination uptake at birth in Ireland was reported to be high (greater than 95%), but this vaccine has not been offered universally as part of the childhood immunisation schedule since 2015.[78] Palivizumab is currently only available to specific groups of infants and children who are deemed to be at high risk of severe RSV disease. Palivizumab uptake rates among the eligible population are not known; available data are limited to quantities dispensed in community pharmacies (see Table 4.15). The dosing schedule for nirsevimab may positively impact on its uptake compared with palivizumab. For example, nirsevimab is typically given as a single dose per RSV season. It may be administered prior to hospital discharge for infants born during the RSV season, or during a single healthcare or GP visit for infants born outside the RSV season. In contrast, palivizumab is given at monthly intervals during the RSV season and therefore a complete course may include up to five doses requiring five separate visits. A further consideration relating to uptake for infants is that the National Immunisation Advisory Committee's (NIAC) recommendations refer to immunisation with nirsevimab for all infants within certain age groups, not only those at risk of severe RSV-related disease. This universal approach is a departure from the previous selective approach for palivizumab, and is therefore likely to impact overall immunisation coverage. For example, uptake may be lower among certain groups such as healthy infants whose parents and or guardians perceive their risk of severe RSV disease to be low.

Antenatal influenza vaccination uptake rates in Ireland may provide relevant insights into potential uptake rates for maternal vaccination against RSV, with the caveat that influenza vaccination is intended to protect the pregnant woman rather than the infant. Available data indicate that seasonal influenza vaccination coverage among pregnant women in Ireland is low in comparison with childhood vaccination coverage, with antenatal influenza vaccination uptake rates of 62% and 42% reported in 2018 and 2020, respectively.[301] Findings from a survey conducted in

one maternity hospital in Ireland suggested that similar uptake rates may be expected for an antenatal vaccine against RSV. Of the 528 women surveyed, 48.5% responded that they would accept an RSV vaccine, if available, and 45.8% were undecided.[302] Factors moderately associated with increased acceptance among respondents were feeling confident in recommended vaccines and feeling that recommended vaccines would protect their baby from illness. Awareness of RSV was low among the women surveyed, with 75.6% of respondents reporting that they had never heard of RSV and only 9.5% of respondents reporting knowledge of the significance of RSV in infancy. However, this survey was conducted in 2018 and 2019, prior to the availability of a maternal RSV vaccine. It is likely that awareness of RSV among pregnant women in Ireland has increased since the time of data collection, given the trend of increasing incidence of RSV and RSV-related hospital admissions over time.

Similarly, in the absence of an established RSV vaccination programme for older adults, uptake data in relation to the HSE's existing influenza and COVID-19 vaccination programmes may be useful indicators of potential RSV vaccine uptake. For the Seasonal Influenza Vaccination Programme, trends in vaccination uptake have shown increases over time and increases with advancing age (see Figure 4.17). Uptake rates of over 70% were observed among adults aged 65 years and older in the seasons from 2020-2021 onwards, although some of this higher uptake may be attributed to the influence of COVID-19. In the 2022-2023 season, the higher uptake was likely influenced by the inclusion of more complete data, since this was the first season in which data relating to the vaccination of healthcare workers and long-term care facility residents were included. On the other hand, COVID-19 vaccination uptake among older adults has declined since 2021, when the programme was first rolled out. Vaccination uptake rates for the most recent 2023-2024 COVID-19 autumn booster campaign were 56.5% in adults aged 65 years and older and 62.2% in adults aged 70 years and older.[230] A number of factors identified as barriers to seasonal influenza vaccine uptake in older adults are also likely relevant barriers to consider in relation to COVID-19 and RSV vaccine uptake. Such barriers include perceived low risk of illness, perceived inconvenience of vaccination, lack of knowledge and or information regarding the pathogen and its associated vaccines, and concerns relating to vaccine effectiveness and safety.[237, 238] Perceived risk of illness may be particularly relevant to an RSV vaccine, in light of the relatively lower documented incidence and burden of RSV-related disease in older adults compared with infants.

The reported Irish data on morbidity and mortality associated with RSV are not linked to immunisation uptake data or other patient risk status data. Therefore, for children, it is not known what proportion of the observed morbidity and mortality

occurred in those at increased risk of severe RSV-related disease or in those who were eligible for immunisation with palivizumab, but had not received it. For older adults, the reported Irish data on morbidity and mortality associated with RSV occurred in a population known to be unvaccinated against RSV. However, data relating to incidence of RSV and associated clinical outcomes lacked information relating to patients' risk status, aside from age (for example, the presence of long-term conditions that increase the risk of severe disease). Additionally, it should be noted in regards to mortality data, that while RSV-related mortality rates reported were relatively low, it is likely these are an underestimate. A 2022 analysis of death certificates in the US between 1999 and 2018 reported an underestimation of RSV mortality in both infants aged under one year and older adults (when compared to excess mortality estimates).[303] While RSV-related mortality reporting has likely improved in recent years, due to improved RSV surveillance and RSV case definitions, the presence of comorbidities and co-infection at time of death may impact mortality reporting. Additionally, it is noted that RSV-mortality measurement may be further complicated in older adults, as deaths associated with respiratory viruses may occur days or weeks after the initial infection, at which time the virus is no longer detectable.[304]

Using HIPE data, the mean annual cost of inpatient bed days related to RSV (which did not include an ICU stay) was approximately €10.4 million per annum in children aged 0 to 4 years, and €400,000 per annum in adults aged 65 years and older. Furthermore, total annual inpatient bed days have increased over time from 2013 to 2022, with the annual cost in 2022 estimated at €17,500,000 in children aged 0 to 4 years and €1,300,000 in those aged 65 years and older. Despite this, it is acknowledged that cost estimates outlined are likely an underestimate as not all RSV cases are laboratory confirmed and some discharges may not be coded. Furthermore, the economic burden associated with RSV includes direct costs resulting from providing care to the patient, such as primary care visits and medical costs, and indirect costs resulting from productivity loss due to illness, or premature death. Although limited research has been published on the total economic burden of RSV in Ireland,[270] international estimates suggest that the burden, including both direct and indirect costs, is likely to be considerable. This is explored further in Chapter 5.

In summary, RSV places a significant burden on secondary healthcare services, with the highest burden seen in infants aged less than one year. RSV poses a particular challenge for paediatric healthcare services as a high proportion of hospital discharges occur in quarter four each year. While testing capacity has increased, the identified data are likely an underestimate of the total burden, as not all RSV cases are laboratory confirmed and some discharges may not be coded.

5 Costing Analysis

Key points

- A costing analysis was conducted to estimate the potential costs and benefits associated with introducing an RSV immunisation programme in Ireland for the 2025-2026 RSV season, specifically considering strategies involving passive immunisation of children (through the use of either a directly acting monoclonal antibody, or through maternal vaccination), and the active immunisation of older adults.
- For children at increased risk of severe disease who are currently eligible for palivizumab, it was estimated that switching to nirsevimab would cost less than current care. Based on an ex-VAT unit cost of €301.12 for nirsevimab, the cost reductions for the 2025-2026 RSV season for these strategies were estimated at €0.85 million (-€1.24 million to -€0.52 million) for infants aged less than one year (n=240) and €2.07 million (-€2.94 million to -€1.35 million) if considering all eligible children aged less than two years (n=581).
- Of the three nirsevimab-based strategies directly targeting the general infant population, assuming an ex-VAT unit cost of €301.12 and an uptake rate of 88%, it was estimated that extending an RSV immunisation programme to include infants in the general population would cost for the 2025-2026 RSV season:
    - €9.3 million to procure and administer nirsevimab, with hospitalisation cost offsets of €6.8 million for the immunisation of infants born during the RSV season (n= 27,807; seasonal immunisation strategy)
    - €19.0 million to procure and administer nirsevimab, with hospitalisation cost offsets of €13.6 million for the immunisation of infants born during the RSV season and those entering their first RSV season (n= 55,678; seasonal and catch-up immunisation strategy)
    - €11.3 million to procure and administer nirsevimab with hospitalisation cost offsets of €8.1 million for the immunisation of infants aged less than four months between October and December (n=33,140; hybrid immunisation strategy).
- Offering a maternal immunisation strategy with RSVpreF to pregnant women who are expected to give birth during the RSV season (n=27,433) and assuming 62% uptake in this cohort, and an ex-VAT unit cost of €165.00, would cost €3.9 million to procure and administer for the 2025-2026 RSV season. These costs were estimated to be broadly comparable to the

hospitalisation cost offsets for this strategy (incremental costs €0.01 million, 95% CI: -€2.24 million to €2.43 million).

- Four strategies considered seasonal vaccination of adults aged 65 years and older (n= 840,830 and assuming 76% uptake), or 75 years and older (n= 381,856 and assuming 87% uptake), with either RSVpreF or RSVPreF3. Assuming an ex-VAT unit cost of €165.00 for both vaccines, vaccination was estimated to cost for the 2025-2026 RSV season:
    - €146.0 million to procure and administer the vaccine for those aged 65 years and older, with hospitalisation cost offsets of €1.2 million for RSVpreF and €1.1 million for RSVPreF3
    - €76.2 million to procure and administer the vaccine for those aged 75 years and older, with hospitalisation cost offsets of €1.0 million for RSVpreF and €0.9 million for RSVPreF3.
- In addition to the costs of the various strategies as outlined, there are implementation costs which would likely apply with the introduction of any new RSV programme for the general infant population or for older adults. These costs, which would include IT system updates, information and training, would likely apply irrespective of the target populations considered and would not vary with immunisation uptake. The cost for the HSE's National Immunisation Office to implement a new programme is estimated at €2.3 million.
- The potential impact on health outcomes and healthcare utilisation of implementing an RSV immunisation programme is subject to considerable uncertainty. Key epidemiological parameters include immunisation coverage, likelihood of hospitalisation and ICU admission, in addition to the clinical effectiveness of the available forms of RSV prophylaxis. Key costs include the estimated costs of the technologies considered and the associated administration fees and labour costs.
- The one-year total costs of these strategies is highly dependent on assuming a favourable product unit cost. Both the product unit costs and their relative costs should be a key consideration in any decision-making and in procurement negotiations with manufacturers. These cost estimates are subject to substantial uncertainty and further real-world evidence may help to reduce this uncertainty.

5.1 Introduction

This chapter outlines the potential costs and effects to the HSE associated with introducing an RSV immunisation programme in Ireland. The immunisation strategies considered in this costing analysis comprise the passive immunisation of children (through use of either a directly acting monoclonal antibody, or through maternal vaccination), and the active immunisation of older adults (through the use of RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®)). As of June 2024, there is no national RSV immunisation programme in place for the general infant and or older adult population. However, children considered to be at high risk of severe RSV disease are eligible to receive palivizumab, a short-acting monoclonal antibody that offers passive immunisation against RSV, funding for which is provided by the HSE. On 18 June 2024, the Minister for Health announced the RSV Immunisation Pathfinder Programme, which is being piloted for the 2024-2025 season.[12] Through this programme, parents of babies (limited to those born from September 2024 to February 2025) will be encouraged to have their babies immunised with nirsevimab before leaving the maternity unit. The purpose of this current rapid HTA is to provide advice to inform a policy decision on immunisation against RSV (in children and older adults) in Ireland for the following season (that is, 2025-2026 season). This chapter provides an estimation of the programme costs and organisational considerations associated with a range of potential immunisation strategies. It should be noted that while the primary purpose of this costing analysis is to estimate the cost of immunisation, this analysis also indicates how immunisation strategies may reduce healthcare utilisation, and as such estimated cost offsets associated with RSV-related hospital costs averted are also presented.

5.2 Methods

For the purpose of this rapid HTA, a costing analysis was conducted in line with the national HTA guidelines for the conduct of Budget Impact Analysis of Health Technologies in Ireland,[305] using Microsoft Excel 2016.

5.2.1 Study perspective

In line with the national HTA guidelines,[305] the costs and benefits of each immunisation strategy were assessed from the perspective of the publicly-funded health and social care system, the Health Service Executive (HSE). As such, only direct medical costs were included. Indirect costs, such as productivity losses associated with morbidity and mortality, or out-of-pocket expenses incurred for patients (for example, travel costs incurred by patients receiving the vaccination), were excluded from the analysis.

5.2.2 Technology

The technology assessed was the introduction of an RSV immunisation programme involving the passive immunisation of children and or the active immunisation of adults aged 65 years and older. The aim of introducing an RSV immunisation programme is to reduce of the burden of RSV in the target populations, and consequently reduce the healthcare burden on the HSE. For strategies concerning the passive immunisation of children against RSV, two products were assessed, specifically:

- nirsevimab (Beyfortus®), a long-acting monoclonal antibody which can be administered directly to the infant, and
- RSVpreF (Abrysvo®), a recombinant bivalent vaccine which may be administered to pregnant women between 24 and 36 weeks' gestation to provide passive immunisation to the infant through transplacental antibody transfer, hereafter referred to as the maternal vaccine.

For strategies concerning the active immunisation of adults aged 65 years and older against RSV, two different vaccines were assessed, specifically:

- RSVpreF (Abrysvo®), which is also authorised for use in adults aged 60 years and older, and
- RSVPreF3 (Arexvy®), a recombinant adjuvanted vaccine which is authorised for use in adults aged 60 years and older.

In October 2023, the National Immunisation Advisory Committee (NIAC) recommended the immunisation of all infants against RSV in their first RSV season, and that, once available, nirsevimab should replace palivizumab for those high-risk infants and children who are currently eligible to receive palivizumab.[11] Based on these recommendations, a number of immunisation strategies targeting (i) infants aged less than one year, and children aged less than two years who are eligible to receive palivizumab, and (ii) the general infant population (that is, those not eligible to receive palivizumab) were modelled; these are outlined in Table 5.1. Included as one of the strategies targeting the general infant population is a strategy offering immunisation to all infants aged less than four months during the period from October to December inclusive (referred to hereafter as the "hybrid" strategy). As outlined in Chapter 4, in recent RSV seasons (2021, 2022 and 2023), the highest notified case rate per 100,000 in the paediatric population occurred in Q4, specifically in November and December. Hospital In-Patient Enquiry (HIPE) data from 2017-2022 show that the majority of hospital discharges (with or without an ICU stay) for children occurred in Q4. Expert opinion received from the EAG for this rapid HTA has suggested that, in Ireland, ICU cases predominantly occur in infants aged less than four months. While hospital discharge data for infants (that is, aged less than one year) were not available further disaggregated by age in months, this

hybrid strategy was costed as an additional alternative approach on the basis of this expert opinion using data relating to infants aged less than one year.

NIAC have also recommended RSV vaccination for adults aged 65 years and older, but specify that, in the event of limited supply of vaccines, priority should be given to those who are at the highest risk of severe RSV disease, including those of more advanced age.[11] As outlined in Chapter 4, data obtained from the Health Protection and Surveillance Centre (HPSC) from 2018 to 2023 indicate that the notified RSV case rate per 100,000 increases with each increasing five-year age band in adults aged 65 years and older (Section 4.3.2). Additionally, the notified RSV ED visit rate per 100,000, and notified RSV hospital admissions rate per 100,000, were observed to increase with each increasing five-year age band in adults aged 65 years and older (section 4.4.2). Based on these data, a strategy targeting the immunisation of adults aged 75 years and older was also included in this analysis.

Table 5.1 Strategies under assessment for both passive and active immunisation against RSV

Intervention	Programme	Eligible population	Immunisation window	Comparator
Passive immunisation of children against RSV				
Nirsevimab	Infants aged <1 year eligible for palivizumab	Infants aged less than one year who are currently eligible to receive palivizumab	▪ Infants born from September to February inclusive offered immunisation at birth. ▪ Infants born prior to the RSV season (that is, aged ≤6 months and entering their first full RSV season) invited for immunisation in September.	Current care
Nirsevimab	Children aged <2 years eligible for palivizumab	Children aged less than two years who are currently eligible to receive palivizumab	▪ Infants born from September to February inclusive during the RSV season offered immunisation at birth. ▪ Infants born prior to the upcoming RSV season and aged less than two years invited for immunisation in September.	Current care
Nirsevimab	Seasonal	All infants at birth	Infants born from September to February inclusive offered immunisation at birth.	Current care
Nirsevimab	▪ Seasonal and ▪ Catch-up	▪ All infants at birth ▪ Infants aged less than one year born outside the RSV season	▪ Infants born from September to February inclusive offered immunisation at birth. ▪ Infants born from March to August inclusive prior to the RSV season invited for immunisation during the weeks immediately preceding the start of the anticipated RSV season.	Current care
Nirsevimab	Hybrid	All infants aged less than four months old between October and December inclusive	▪ Infants born from September to December inclusive offered immunisation at birth. ▪ Infants born from June to August inclusive prior to the RSV season invited for immunisation during the weeks immediately preceding the start of the anticipated RSV season.	Current care
RSVpreF	Maternal	Pregnant women (between 24 and 36 weeks gestation) who are due to give birth during the RSV season	Maternal vaccine offered between 24 and 36 weeks' gestation, where due date is expected within the proposed RSV season (defined as September to February inclusive).	Current care
Active immunisation strategies for adults aged 65 years and older against RSV				
RSVpreF	Seasonal	Adults aged ≥65 years	September to February inclusive	No immunisation
RSVpreF	Seasonal	Adults aged ≥75 years	September to February inclusive	No immunisation
RSVPreF3	Seasonal	Adults aged ≥65 years	September to February inclusive	No immunisation
RSVPreF3	Seasonal	Adults aged ≥75 years	September to February inclusive	No immunisation

Key: LRTD – lower respiratory tract disease; RSV – respiratory syncytial virus.
Current care: Palivizumab offered to children aged <2 years who are at increased of severe RSV-associated LRTD; no immunisation offered to infants in the general population, that is, not identified to be at increased risk of severe RSV-associated LRTD.
Notes: Recommendations on the use of palivizumab prophylaxis can vary. While individual hospitals may follow their own local guidance or formulary, the NIAC Immunisation Guidelines for RSV outline specific paediatric populations where palivizumab prophylaxis is recommended.[76]

5.2.3 Choice of comparators

For children considered to be at increased risk of severe RSV disease, at the time of this assessment, the standard of care was palivizumab, a short-acting monoclonal antibody that offers passive immunisation against RSV. As previously outlined in Chapter 2 (section 2.5.2), palivizumab may be administered at monthly intervals throughout the RSV season. Infants in the general population (that is, those not identified to be at risk of severe RSV disease) are currently not immunised against RSV. All passive immunisation strategies targeting the paediatric populations were compared against the existing standard of care (Table 5.1).

In the case of active immunisation of adults aged 65 years and older against RSV, both technologies under assessment (that is, RSVpreF and RSVPreF3) were compared against the current standard of care, that is, no immunisation (Table 5.1).

5.2.4 Setting for delivery

As previously outlined, at the time of this assessment there was no national RSV immunisation programme in place. In this analysis, certain assumptions were made for the purpose of the costing exercise regarding the most appropriate setting within which any immunisation programme considered could be delivered. This analysis considered a range of RSV immunisation strategies, which targeted a number of eligible populations. While the assumptions are outlined below, these are expanded upon in section 5.2.9.

- For this costing analysis, it was assumed that immunisation against RSV would be offered to eligible paediatric populations in one of two settings:
    - Eligible infants born during the RSV season would be offered immunisation in the days after birth. It was proposed that, where possible, immunisation should be offered one day after birth, during the routine clinical assessment conducted by midwives. This assessment takes place in the maternity unit and or hospital, while the infant is an inpatient. In situations where the infant has already been discharged, or is delivered by homebirth, it was proposed that a parent/guardian attends the hospital with the infant for this clinical assessment. Alternatively, immunisation could be offered alongside the newborn heel prick test, which is offered as part of the National Newborn Bloodspot Screening Programme (NNBSP), and typically takes place 72-120 hours after birth.[306] If offered alongside the newborn heel prick test, it was anticipated that immunisation would be delivered while the infant is in a maternity unit and or hospital, or by public health nurses operating through Local Health Offices (LHOs).

- For infants aged less than one year, who are born outside of the RSV season, it was assumed that they would be invited for immunisation against RSV during the weeks immediately preceding the start of the anticipated RSV season, with the goal that uptake for this cohort is completed prior to the start of the RSV season. For the purposes of this costing analysis, it was proposed that these infants (born outside of the RSV) would be offered immunisation in a primary care setting, through a registered GP.
- It was assumed that infants included in the hybrid approach would receive immunisation either as part of a seasonal cohort (born from September to February inclusive) or a catch-up cohort (born from June to August inclusive); immunisation would be delivered in the appropriate setting as outlined above.
- In the case of infants aged less than one year who are currently eligible to receive palivizumab, and who are born during the RSV season, it was assumed that immunisation against RSV would be offered in the days following birth, or at the earliest appropriate opportunity. Where born outside the RSV season, it was assumed that they would be invited for immunisation against RSV between during the weeks immediately preceding the start of the anticipated RSV season, again with the goal that uptake is completed prior to the start of the RSV season and that immunisation against RSV would be offered in the same setting in which palivizumab is currently offered (typically secondary care for those that are hospitalised or initiating therapy, although therapy can also be initiated in primary care).
- In the case of children aged one to two years, who are currently eligible to receive palivizumab, it was proposed that immunisation against RSV would be offered during the weeks immediately preceding the start of the anticipated RSV season in the same setting in which palivizumab is currently offered.

- In the case of maternal immunisation, it was assumed that pregnant women would be offered the maternal vaccine by their registered GP.

- In the case of strategies considered for older adults, it was assumed that vaccination against RSV would take place in primary care and community settings which currently offer seasonal vaccination against other respiratory diseases, such as COVID-19 and seasonal influenza. These currently include GP practices and pharmacies that offer vaccination services by authorised community pharmacists. Vaccination against COVID-19 and seasonal influenza in the community is also provided by HSE Vaccination Teams who currently go to long-term care facilities (LTCFs) to offer vaccination to eligible residents.

5.2.5 Time horizon

The time horizon represents the timeframe over which resource use is planned. This costing analysis was conducted to estimate the implications of introducing an RSV immunisation programme for one year only. While the potential costs and effects associated with introducing the included strategies as part of an RSV immunisation programme cover the period of one year, the effects on healthcare utilisation are anticipated to be seen primarily over the 2025-2026 RSV season.

5.2.6 Measurement and valuation of resources

Estimation of costs was carried out using a range of methods as appropriate to each item.[305] In the case of estimation of parameters such as target populations, incidence and healthcare burden, these were informed by national data, including data from the Central Statistics Office (CSO), Healthcare Pricing Office (HPO), HPSC, HIPE and Primary Care Reimbursement Service (PCRS). Where limited data were available (such as maternal vaccine uptake rates), these were supplemented by expert opinion from within the HTA team and relevant external stakeholders. Where possible, data from international sources (for example, nirsevimab uptake rates in the paediatric population currently eligible to receive palivizumab) were used to validate assumptions. Specific data used to inform resource use and valuation estimates are described separately for each item below.

5.2.7 Epidemiological inputs

Target populations

There were a number of different target populations considered for each of the strategies in this analysis.

Children at increased risk of severe lower respiratory tract disease associated with respiratory syncytial virus (RSV)

In Ireland, palivizumab is currently recommended and funded for identified subgroups of children aged less than two years who are considered at risk of severe LRTD associated with RSV.[11] This analysis considered replacing current standard of care (that is, immunisation with palivizumab at monthly intervals (up to a maximum of five doses) for the duration of the RSV season), with nirsevimab, which is administered as a single dose prior to the start of the RSV season or as soon as possible after the child is born.

This costing analysis considered two possible alternative strategies for those currently eligible to receive palivizumab, that is, switching to nirsevimab for:

- eligible infants aged less than one year only
- all eligible children aged less than two years.

Data obtained from the PCRS from 2013 to 2023 were used to ascertain the number of unique patients in receipt of palivizumab annually. Based on CSO population projections,[307, 308] the number of infants who may be eligible to receive palivizumab in 2025 was estimated to be 240 for those aged less than one year, and 581 when considering all eligible children aged less than two years.

General infant population

Data obtained from the CSO were used to estimate the projected infant population for this analysis.[309, 310] Three strategies in this analysis considered extension of immunisation with nirsevimab to infants who are not at increased risk of severe LRTD associated with RSV (that is, the general infant population):

- The first strategy (that is, the seasonal strategy) considered immunisation with nirsevimab for all infants born during an RSV season in the days following birth, who are not currently considered eligible for palivizumab. In this analysis, an RSV season was defined as the six-month period from September to February inclusive. This time was selected owing to the earlier shift in seasonality of RSV-notified cases observed in Ireland in recent years (as outlined in Chapter 4). The total infant population eligible for this seasonal strategy was estimated to be 27,807.[309, 310]
- The second strategy included both (i) the seasonal strategy as above and (ii) a 'catch-up' strategy of immunisation with nirsevimab for infants born between March and August (that is, who are aged less than six months at the start of the RSV season), and not eligible to receive palivizumab. It was assumed that the catch-up strategy would be offered during the weeks immediately preceding the start of the anticipated RSV season. The total infant cohort eligible for immunisation as part of this strategy was estimated to be 55,678; this included those eligible for the seasonal strategy (27,807 infants) and the catch-up strategy (27,871 infants).[309, 310]
- The third strategy (that is, the hybrid strategy) considered the immunisation of all infants aged less than four months during the period from October to December 2025 inclusive, who are not currently eligible to receive palivizumab. As outlined in Chapter 4, in recent RSV seasons (2021, 2022 and 2023), the highest notified case rate per 100,000 in the paediatric population occurred in Q4, specifically in November and December. Additionally, from 2017-2022, the majority of hospital discharges (either with or without an ICU stay) for infants occurred in Q4. Expert opinion received from the EAG for this rapid HTA has suggested that, in Ireland, ICU cases predominantly occur in infants aged less than four months. While hospital discharge data for infants (that is, children aged less than one year) were not available further disaggregated by age in months, this hybrid strategy was costed on the basis

of this expert opinion. This population included infants born from June to December inclusive, with the eligible population estimated to be 33,140 infants comprising 14,271 infants born between June and August inclusive (prior to the RSV season) and 18,869 infants born between September and December).[309, 310] As per the seasonal and catch-up strategies outlined above, it was assumed that infants born during the RSV season would be immunised prior to hospital discharge while those born prior to the RSV season would be immunised during the weeks immediately preceding the start of the anticipated RSV season.

Pregnant women between 24 and 36 weeks' gestational age

The maternal strategy considered offering the maternal vaccine to pregnant women (between 24 and 36 weeks' gestation) who are expected to give birth during the RSV season. This strategy would confer passive immunity to infants due to be born from September to February inclusive.

To account for the potential for multiple births from a single pregnancy, data from the CSO for 2025 were used to estimate the number of maternities expected,[311] that is, the number of pregnancies resulting in the birth of one or more children. The number of maternities corresponding with babies born between September and February was estimated to be 27,433, that is, the population eligible to receive vaccination in this analysis. Accordingly, this was the estimated population to which costs associated with roll-out and administration for this maternal strategy relate. The infant population to whom the benefits of maternal vaccination are conferred (such as reduced risk of infection, hospitalisations with or without ICU, and morbidity), was estimated at 27,927.[309, 310] This population represents all infants born during the RSV season, including those at increased risk of severe disease associated with RSV and therefore otherwise eligible for palivizumab in their first RSV season, and those infants not identified as being at increased risk of disease (that is, the general infant population).

For simplicity, this strategy is limited to immunisation of pregnant women with the maternal vaccine, that is, it does not include offering nirsevimab at birth to infants born to mothers who do not avail of the vaccine or to infants who are born within 14 days of the mother receiving the maternal vaccine.

Adults aged 65 years and older

Active immunisation strategies considered in this analysis comprised:

- adults in the general population aged 65 years and older
- adults in the general population aged 75 years and older.

Using data from the CSO, the number of adults aged 65 years and older for 2025 was estimated to be 840,830, and 381,856, for those aged 75 years and older.[308]

Immunisation uptake

Infants at increased risk of severe lower respiratory tract disease (LRTD) associated with respiratory syncytial virus

Irish data relating to palivizumab uptake rates in eligible infants are not recorded. In the Galicia region of Spain, for the 2023-2024 season, nirsevimab was offered to infants considered at increased risk of severe RSV (that is, those eligible for palivizumab). Reported uptake of nirsevimab was 97%.[312] In this analysis, an uptake of 100% was assumed in the base-case analysis for infants aged under one year, and the scenario analysis for children aged under two years at increased risk of severe LRTD associated with RSV, to reflect a maximum cost to the HSE of providing nirsevimab to these cohorts.

General infant population

In Ireland at the time of this assessment, there are no vaccines from the national primary childhood immunisation schedule routinely offered to all infants in the days following birth; the earliest visit in this schedule takes place two months post-birth, where four vaccines are scheduled for administration, specifically the '6-in-1 vaccine', MenB vaccine, PCV vaccine, and rotavirus oral vaccine.[313] As outlined in Chapter 4, the HPSC provides quarterly data related to primary childhood immunisation uptake for all vaccines offered.[216] Considering data from 2018 to 2023 (Q1-Q3 available only for 2023), the national rate of primary childhood immunisation uptake in Ireland at 12 months across all vaccines was estimated to be 88.1%. This figure was used as the base-case value for nirsevimab uptake for all strategies directly targeting the general infant population in the costing analysis.

Antenatal vaccine uptake

No international data were identified relating to the uptake of maternal RSV vaccine.

In Ireland, pertussis, influenza, and COVID-19 vaccinations are recommended for women during pregnancy.[218, 314] The pertussis vaccine is typically administered by the patients' registered GP, and the vaccine is free (at the point of administration) during pregnancy. The PCRS schedule does not currently list an administration fee for the pertussis vaccine; however, it is noted that GPs are eligible to claim an administration fee of €28.50 in situations of disease outbreak.[315, 316] Pregnant women are classified as a group at increased risk of severe disease and adverse pregnancy outcomes from influenza[223] and SARS-CoV-2 infection.[218] As such, they

may also avail of these vaccines free of charge at the point of administration through either a registered GP or a community pharmacy.[317, 318] However, in Ireland, there are very limited nationally collected data relating to uptake of vaccines routinely offered to pregnant women (seasonal influenza, COVID-19, pertussis). A report from the World Health Organization (WHO) cited maternal influenza vaccination uptake data for Ireland of 42.1% (2020) and 62% (2020). These data represent administrative influenza coverage reported annually through the WHO/UNICEF Joint Reporting Form on Immunization by groups targeted for vaccination by the country.[224] Two published cohort studies relating to uptake of maternal vaccinations in Ireland were identified, one of which reported a seasonal influenza vaccine uptake rate of 57% and a COVID-19 vaccine uptake rate of 22% in a sample of 588 pregnant women attending the National Maternity Hospital, Dublin over a two week period in 2022.[319] The second study was conducted over the 2017-2018 influenza season (September through March) and reported an influenza vaccine uptake rate of 61.7%, and pertussis vaccine uptake rate of 49.9% in a sample of 241 pregnant women.[320] A 2024 ECDC report on COVID-19 vaccination coverage during the 2023-2024 season reported that 19.6% of pregnant women in Ireland received a single dose of a COVID-19 vaccine between September 2023 and March 2024.[227] This estimate is based on data collected through TESSy, which the HPSC reports to, which are collected through the CoVax system.[228] However, as outlined in section 4.6.1, there is some uncertainty with this estimate given how this information is recorded on the CoVax system.

Based on the limited Irish data available, uptake of the antenatal vaccine was estimated to be 62% in the base-case scenario for a maternal immunisation strategy. This estimate would most likely reflect maximum vaccine uptake, and so reflect a realistic maximum cost to the HSE of a maternal immunisation programme. Considering that this is a new technology and the uncertainty in relation to antenatal vaccine uptake rates, a range of other uptake rates (range 42% to 62%) were considered in the scenario analyses.

Adults aged 65 years and older

No Irish or international data relating to the uptake rate of either RSVpreF or RSVPreF3 were identified. In the absence of these data, it was assumed that Irish data for seasonal respiratory infections, such as seasonal influenza, would provide the most reliable estimate of projected RSV vaccination uptake in this population. Data obtained from the HPSC reported that seasonal influenza vaccine uptake in all adults aged 65 years and older was 75.7% for the 2022-2023 influenza season (week 38-week 8)[321] and 75.5% for the 2023-2024 influenza season (week 38-week 8),[321] with a total vaccine uptake in this age group reported as 76.5% between September 2022 and August 2023.[235] These data also reported seasonal influenza vaccine uptake in adults aged 75 years and older as 87.1% between September 2022 and August 2023.[235] These figures reflect the administration of all influenza vaccines funded for this age group through the HSE's Seasonal Influenza Vaccination Programme across all settings, including GP practices, community pharmacies, hospitals and long-term care facilities. While these data exclude influenza vaccination paid for privately, it is noted that all adults aged 65 years and older are currently offered seasonal influenza vaccination free of charge at the point of administration under this vaccination programme. It was therefore assumed that these figures represent total uptake in this population. Based on the average uptake in adults aged 65 years and older for the most recent winter influenza seasons (2022-2023 and 2023-2024), the current influenza vaccination uptake rate was calculated to be 76%, with this rate taken as the base-case value for strategies targeting adults aged 65 years and older in the analyses. For strategies targeting adults aged 75 years and older, a base-case value of 87% was adopted. Results associated with a range of vaccination uptake rates were considered to account for uncertainty in these estimates.

Clinical efficacy or effectiveness of intervention

Children at increased risk of severe lower respiratory tract disease associated with respiratory syncytial virus

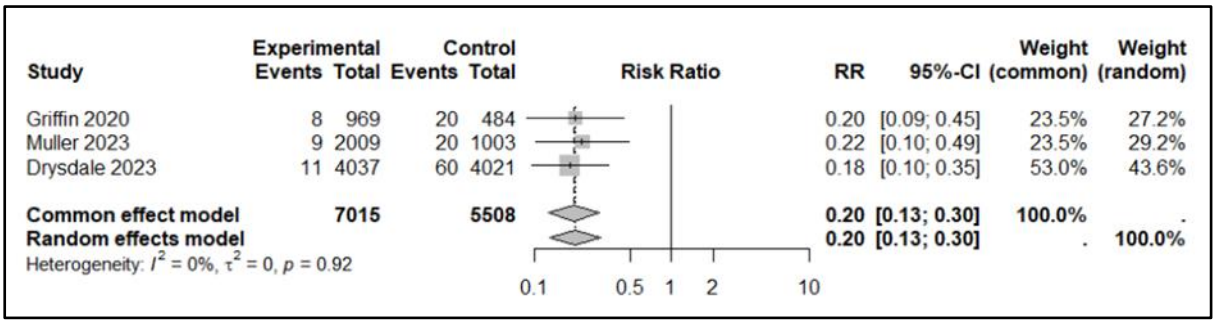
The effectiveness of palivizumab at reducing hospitalisation due to RSV infection used in the analysis was 56% (95% CI: 36% to 70%), as reported by a Cochrane review published in 2021.[322] The included studies in this Cochrane review were predominantly conducted in children with a high risk of severe LRTD associated with RSV due to comorbidities like bronchopulmonary dysplasia and congenital heart disease. In the absence of data on the effectiveness of nirsevimab specifically in this population, it was assumed that both palivizumab and nirsevimab were equally effective in this cohort.

General infant population

As previously discussed in Chapter 3, the efficacy of nirsevimab has been assessed in a number of clinical trials. For this costing analysis, data from D5290C00003,[109] MELODY[323] and HARMONIE[112] trials specific to reduced hospitalisations due to RSV-associated LRTI were included. The case definition of this end point in the HARMONIE trial differed slightly to that of the D5290C00003 and MELODY trials. Data regarding the efficacy of nirsevimab at reducing RSV-associated hospitalisations at 150 days post-immunisation (where all cases had tested positive for RSV) were pooled by the HIQA evaluation team. The pooled relative risk was 0.20 (95% CI: 0.13 – 0.30) as seen in Figure 5.1, corresponding to an efficacy of 80% (95% CI: 70% to 87%). Of note, all of these three RCTs excluded infants who were eligible to receive palivizumab (that is, infants at high risk of severe disease from RSV).

This estimate is supported by available real-world evidence for the 2023-2024 season from Galicia, Spain which reported that the effectiveness of nirsevimab in reducing RSV-associated LRTI hospitalisations (in both seasonal and catch-up cohorts combined) was 82.0% (95% CI: 65.6 to 90.2).[312] Similarly, another retrospective cohort study conducted in Catalonia, Spain during the 2023-2024 RSV season reported that the effectiveness of nirsevimab against hospital admission (for infants born between April and September 2023) was 87.6% (95% CI: 82.1 to 91.4).[324]

Figure 5.1 Forest plot of pooled studies to provide an estimate of the relative risk of RSV-associated hospitalisations in infants at 150 days post-immunisation with nirsevimab



Key: RR – relative risk
Note: Griffin 2020 = D5290C000030;[109] Muller 2023 = MELODY;[323] Drysdale 2023 = HARMONIE.[112]

Maternal immunisation

In the case of the maternal vaccine, efficacy endpoints are not directly comparable to those of nirsevimab. In the base-case analysis, the estimate of vaccine efficacy of RSVpreF was taken from the interim analysis of the MATISSE trial at 150 days post birth; this was reported as 70.9% (95% CI: 44.5% to 85.9%) and reflects the

efficacy of RSVpreF against RSV-positive severe medically attended LRTI.[126] Data reported in the MATISSE interim analysis indicate that the maternal vaccine does not show improved efficacy against RSV-associated hospitalisations over and above that demonstrated for reducing incidence of RSV-positive severe medically attended LRTI. As such, the effectiveness of the maternal immunisation strategy is based on reduced incidence of severe RSV, rather than reduced RSV-associated hospitalisations. In this analysis, it was assumed that reductions in hospitalisation and admission to ICU are directly proportional to reductions in incidence.

Adults aged 65 years and older

The efficacy of RSVpreF was taken from the ongoing RENOIR phase 3 RCT.[149] At the time of marketing authorisation, the reported vaccine efficacy of RSVpreF against the first episode of RSV-associated LRTI with three or more signs or symptoms (experienced for 24 hours or more) was 88.9% (95% CI: 53.6% to 98.7%) in adults aged 60 years and older.[9] The estimate of vaccine efficacy of RSVPreF3 against the first RSV-associated LRTD (including where three or more symptoms were experienced for 24 hours or more) in adults aged 60 years and older was taken from the ongoing AReSVI-006 phase 3 RCT, and reported as 82.6% (96.95% CI: 57.9% to 94.1%).[42] No data exist to indicate the efficacy of either RSV vaccine specifically against RSV-associated hospitalisations in older adults. As previously outlined, in this analysis, it was assumed that reductions in hospitalisation and admission to ICU are directly proportional to reductions in incidence.

Table 5.2 Summary of estimates of efficacy or effectiveness used in the base-case analyses

Technology	Programme	Estimate	Source
Palivizumab	Children at increased risk of severe LRTD associated with RSV who are currently eligible to receive palivizumab	Outcome: Hospitalisation due to RSV infection Follow-up: 2 years Clinical efficacy / effectiveness: 56% (95% CI: 36% to 70%)	Cochrane systematic review (2021)[322]
Nirsevimab	Children at increased risk of severe LRTD associated with RSV who are currently eligible to receive palivizumab	Clinical efficacy / effectiveness: 56% (95% CI: 36% to 70%)	As above. Nirsevimab assumed not to have any additional benefit over palivizumab in children in this cohort.
Nirsevimab	• Seasonal immunisation of infants • Seasonal and catch-up immunisation of infants • Hybrid strategy for immunisation of infants	Outcome: Hospitalisation for RSV-associated LRTI Follow-up: 150 days Clinical efficacy / effectiveness: 80% (95% CI: 70% to 87%)	Pooled estimate using data from: •D5290C000030 RCT[109] •MELODY RCT[323] •HARMONIE RCT[112]
RSVpreF	Maternal immunisation	Outcome: Medically-attended severe RSV-associated LRTI Follow-up: 150 days VE: 70.9% (95% CI: 44.5% to 85.9%)	MATISSE phase 3 RCT[126] Interim results used as final study results are as yet unpublished (June 2024).
RSVpreF	• Adults aged ≥ 65 years • Adults aged ≥75 years	Outcome: First episode of RSV-LRTI with ≥3 signs / symptoms Follow-up: from 14 days after vaccination through to the end of the first RSV season (defined as a minimum of about 8 weeks after the actual RSV epidemic ended in a given region) VE: 88.9% (95% CI: 53.6% to 98.7%)	RENOIR phase 3 RCT[149] Trial ongoing, interim results used.
RSVPreF3	• Adults aged ≥ 65 years • Adults aged ≥75 years	Outcome: RT-PCR–confirmed RSV-related LRTD. Follow-up: median 6.7 months (median) VE: 82.6% (96.95% CI: 57.9% to 94.1%)	AReSVI-006 phase 3 RCT[42] Trial ongoing, interim results used.

Key: CI – confidence interval; LRTD – lower respiratory tract disease; LRTI – lower respiratory tract infection; RCT – randomised control trial; RSV – respiratory syncytial virus; RT-PCR – reverse-transcriptase polymerase chain reaction; VE – vaccine efficacy.

Health outcomes

As reported in Chapter 4, RSV-related health outcome data were sourced from the HPSC and HIPE system. These data were used in this analysis to ascertain the potential reduction in:

- number of notified RSV cases
- number of hospital discharges and associated bed days in patients with a primary diagnosis of RSV
- number of hospital discharges that include an ICU stay and associated bed days in patients with a primary diagnosis of RSV, and
- mortality related to RSV.

It should be noted that RSV-related health outcome data specifically relating to paediatric populations at increased risk of disease were not available. As such, in this analysis, infants at increased risk of RSV disease were assumed to have the same risk of infection and hospitalisation as that observed in the general paediatric population. Similarly, all infants aged less than one year were assumed to have the same risk of disease and hospitalisation, regardless of month of birth, or age during the RSV season.

5.2.8 Cost inputs

Monoclonal Antibodies

Unit costs

Costs relating to palivizumab usage were calculated using data obtained from the PCRS, and in accordance with the National Guidelines for Inclusion of Drug Costs for Economic Evaluation.[325] The unit costs of palivizumab were calculated as €454.65 per 50mg/ml vial, and €800.65 per 100mg/ml vial. Palivizumab is currently reimbursed by the PCRS through the High Tech Medicinal Products Scheme (referred to as the High Tech scheme hereafter).[326] Using data provided by the PCRS from 2019 to 2023, and accounting for all necessary mark-ups, rebates and patient care fees for products dispensed under the High Tech scheme, the weighted average cost per vial of palivizumab (of any strength) to the payer was estimated, both for infants aged less than one year, and children aged less than two years. The average number of vials dispensed per patient annually in the community setting was estimated to be 3.3 vials in infants aged less than one year, and 3.4 vials in children aged less than two years. Expert opinion received from the EAG for this rapid HTA has suggested that, in practice, those commencing palivizumab receive an initial dose in hospital, with subsequent doses delivered within a community setting. As such, it was considered as part of the costing that infants aged less than one year

also receive this additional dose of palivizumab delivered in hospital in all scenarios assessed, corresponding with an average of 4.3 vials aged less than one year. Additionally, under the High Tech scheme, a patient care fee may be payable to a patient's registered pharmacy in the event where medicinal products are not dispensed, for up to a maximum of three consecutive months after the medicinal product was last dispensed.[327] As this analysis aims to estimate the plausible maximum cost to the HSE of an intervention, it was assumed that an additional three patient care fees for non-dispensed items would be paid by the HSE to a pharmacy for each patient as part of this primary care reimbursement agreement. In the base-case analysis, the annual cost to the payer (HSE) in 2025 was estimated to be €3,175.72 (excluding VAT) per infant aged less than one year and eligible to receive palivizumab, and €2,860.20 (excluding VAT) per child aged less than two years and eligible to receive palivizumab (see Table 5.3 below).

As of May 2024, nirsevimab is not currently available in Ireland, and as such there is no Irish list price to inform the costing analysis. Contract prices were identified for both Spain and the USA for 2023 and, in both countries, the same contract price applied to both strengths of nirsevimab available (50mg and 100mg dose). In Spain, the reported contract price for one healthcare region for the 2023-2024 RSV season was €209 per dose.[328] In the USA, the price ranged from $395 per dose (CDC contract price) to $495 per dose (private purchase price).[329] In France, the retail price listed for both strengths of nirsevimab was €393.20 (excluding VAT) in 2023,[330, 331] although there is no literature available to indicate whether this was the contract price paid by the French government per unit of nirsevimab procured as part of the pilot infant RSV immunisation programme implemented over the 2023-2024 season. In the absence of an Irish list-price, the unit cost per dose of nirsevimab was estimated to be €301.12 (excluding VAT) in the base-case analysis for all strategies. This cost was estimated based on an average of the Spanish contract price and French private purchase price. Given the uncertainty regarding the potential unit cost of nirsevimab, a range of unit costs above and below the base-case price were also considered, using the aforementioned Spanish and French prices as the lower and upper bounds assessed (see Table 5.4 below).

In the base-case analyses for all immunisation strategies targeting infants and children, it is assumed that nirsevimab would be centrally procured following a competitive tender process, and so would not be subject to additional rebates, mark-up or fees associated with reimbursement under the High Tech scheme, as is currently the case for palivizumab.

Both palivizumab and nirsevimab are subject to a standard VAT rate of 23%, as they are non-oral medicines.[332, 333]

Administration fees

No administration fee was applied with respect to palivizumab administration for hospitalised children and those receiving palivizumab when attending as a hospital outpatient as it was assumed that the admission or outpatient appointment was not for the sole purpose of palivizumab administration.

An at-home paediatric programme has been implemented in Ireland by the manufacturer of palivizumab since 2008. Families collect the drug on a monthly basis from their community pharmacy, with trained nurses subsequently visiting the infant's home to administer the drug.[334] It is unclear how long this arrangement might continue, although there is no indication that it will cease in the short term. It was assumed that all infants requiring palivizumab in the community would avail of the at-home programme. The cost of providing this at-home administration service is assumed to be incorporated into the list price charged by the manufacturer, and as such, no additional administration fees were assumed payable by the HSE in this costing analysis where palivizumab is delivered in the community setting.

Table 5.3 Summary of the estimated annual cost of immunising one child with palivizumab

Immunisation with palivizumab	Annual cost of immunising one infant excluding VAT (€)	Annual cost of immunising one infant including 23% VAT (€)	Administration fee (€)	Total annual cost of immunising one infant (€)
Infants aged <1 year of age at increased risk of severe LRTD associated with RSV	3,175.72	3,911.46	0	3,911.46
Children aged <2 years of age at increased risk of severe LRTD associated with RSV	2,860.20	3,517.45	0	3,517.45

Key: LRTD – lower respiratory tract disease; RSV – respiratory syncytial virus; VAT – value-added tax
Note: Annual drug cost uses a weighted average cost per vial (50mg/ml and 100mg/ml) and assumes an average of 4.3 vials per season for infants aged less than one year and 3.5 vials for children aged one to two years based on PSRS data.

For the immunisation strategies targeting children in this costing analysis, it was proposed that nirsevimab be administered in two different settings. In the case of infants born during the RSV season, it was assumed that infants would receive a single dose of nirsevimab in the days after birth, either (i) as part of a clinical assessment undertaken in a maternity unit and or hospital on the second day of life, or (ii) concurrently with the newborn heel prick test, which is conducted as part of the National Newborn Bloodspot Screening Programme. At present, the newborn

heel prick test is conducted by staff midwives in a maternity unit and or hospital, or by public health nurses or community midwives if an infant has already been discharged.[306] In either setting, immunisation would be delivered by HSE staff, and so it was assumed that no administration fee would be payable. Incremental labour costs associated with this additional workload are considered in section 5.2.10 below.

In the case of eligible infants born outside of the RSV season, for all strategies, it was assumed that nirsevimab would be administered in the primary care setting during the weeks immediately preceding the start of the RSV season. In the base-case analyses, an administration fee of €19.73 payable by the HSE was assumed for this cohort. This fee was previously estimated by HIQA as an average of all contractual payments currently made to GPs for the current national childhood immunisation programmes.[335] To reflect uncertainty in relation to this estimate, the administration fee payable per unit of nirsevimab delivered was varied 20% above and below the mean assumed value of €19.73.

As it cannot be assumed that an at-home paediatric programme (such as that implemented by the manufacturers of palivizumab) will be implemented by the manufacturers of nirsevimab, this administration fee was also applied to the immunisation strategy targeting children at increased risk of severe LRTD associated with RSV who are born outside of the RSV season, where it was proposed that nirsevimab may be administered in a primary care setting. This assumption reflects a maximum realistic cost to the HSE of switching from palivizumab to nirsevimab in this cohort.

Table 5.4 Summary of the cost of immunising a child with nirsevimab at various product costs

Immunisation with nirsevimab	Cost of immunising one infant excluding VAT (€)	Cost of immunising one infant including 23% VAT (€)	Administration fee (€)	Total cost* of immunising one infant (€)
Children born during the RSV season, where immunisation is offered in the days following birth				
Cost 1	209.00	257.07	0	257.07
Cost 2	255.06	313.72	0	313.72
Cost 3 - Base-case analysis	301.12	370.38	0	370.38
Cost 4	347.18	427.03	0	427.03
Cost 5	393.24	483.69	0	483.69
Children born outside the RSV season, where immunisation is offered prior to the anticipated start of the RSV season				
Cost 1	209.00	257.07	19.73	276.80
Cost 2	255.06	313.72	19.73	333.45
Cost 3 - Base-case analysis	301.12	370.38	19.73	390.11
Cost 4	347.18	427.03	19.73	446.76
Cost 5	393.24	483.69	19.73	503.42

Key: RSV – respiratory syncytial virus; VAT – value-added tax.
*Incremental labour costs for HSE staff administration considered separately.

Vaccines

Unit costs

In March 2024, both RSVpreF and RSVPreF3 became available for private purchase in Ireland, on foot of a prescription. As of May 2024, the current list price of RSVpreF (Abrysvo®) is currently unknown, while manufacturers have stated that the Irish list price of RSVPreF3 (Arexvy®) is €165, excluding VAT. In May 2024, both products were listed for purchase from wholesalers at a cost of €194.12 (which includes wholesale mark-up). Specific detail relating to the percentage mark-up applied is not available, however it has been assumed to be identical for both products. As such, the list price of RSVPreF3 (that is, €165) was taken as the unit cost for both vaccines in the base-case analyses.

At present, two respiratory vaccines are offered as part of seasonal immunisation programmes (that is, the seasonal influenza and COVID-19 vaccines).[317, 318] Both vaccines may be administered in primary care settings, such as GP practices and through community pharmacies.[317, 318] Given that there are two RSV vaccines authorised for use in adults aged 60 years and older, of which one (that is, RSVpreF) could be adopted as part of an immunisation programme targeting infants, it was assumed that a competitive tender process may take place as part of negotiations

for a RSV immunisation programme procurement contract. As such, further analyses were conducted exploring a range of potential lower unit costs for these RSV vaccines. As non-oral medicinal products, vaccines are subject to a standard value-added tax (VAT) rate of 23%,[332, 333] which was included in the costing analysis.

Administration fees

While vaccines are offered free of charge at the point of administration to those specific populations deemed eligible for seasonal immunisation programmes, vaccination primary care contractors administering these vaccines may claim an administration fee from the HSE.[317, 318] In the case of influenza vaccines delivered during the 2023-2024 season, the vaccine administration fee paid by the HSE to both GPs[317] and pharmacists[318] was set at €15 per vaccine delivered. In addition, these vaccination primary care contractors were also eligible for a payment of €100 for every 10 unique patients to whom an influenza vaccine was administered. Previous research carried out by the HIQA evaluation team has estimated that, based on the number of GP practices and pharmacies in Ireland, the average cost to the HSE of administration for seasonal influenza vaccinations is approximately €24.88 (95% CI: 24.80 to 24.99) per individual.[336] In the case of the COVID-19 vaccine, both GPs and pharmacists received a fee of €25 per vaccine administered during the 2023-2024 season.[317, 318] On the basis of these existing administration fee agreements, an administration fee of €25 was assumed in the base-case analyses for delivery of RSV vaccines to eligible older adults. See Table 5.5.

In the case of the administration of seasonal respiratory vaccinations to pregnant women, such as influenza and COVID-19, the administration fee payable by the HSE to a vaccinating GP or pharmacist is identical to that payable for vaccination of older adults,[317, 318] that is, €25. As such, for the base-case analysis, a €25 administration fee (payable to the vaccinator) was also assumed for maternal immunisation.

Table 5.5 Summary of the cost of immunising one pregnant woman (with the maternal vaccine, that is, RSVpreF) or older adult (with RSVpreF or RSVPreF3) at various vaccine prices

Vaccine unit dose cost (€)	Vaccine unit dose cost with 23% VAT (€)	Administration fee (€)	Total cost of vaccinating one individual (€)
165.00 – Base-case analysis	202.95	25.00	227.95
160.00	196.80	25.00	221.8
155.00	190.65	25.00	215.65
150.00	184.50	25.00	209.5
145.00	178.35	25.00	203.35

Key: VAT – value-added tax.

Hospital discharges and associated costs

The average cost of a hospital episode associated with RSV was estimated using HIPE data provided by the HPO, as outlined in Chapter 4. Data pertaining to discharges with a primary diagnosis of RSV in those aged 0 to 4 years (for the years 2013 to 2022) were used to calculate an average cost of a hospital episode (excluding the year 2020 as these figures were not considered representative, due to the COVID-19 pandemic and likely potential changes in transmission patterns). The average cost of a hospital episode was estimated to be €9,739. The average cost for the subset of hospital episodes which included an ICU stay was €31,453. The HIPE data do not distinguish between those at increased risk of severe disease and those in the general population. As hospital costs were not available disaggregated by age for those aged less than four years, the same weighted average cost per discharge was used across all immunisation strategies targeting children.

The average length of stay in hospital (weighted for discharges with and without an ICU stay) was estimated to be 4.3 days for infants aged less than one year old, and 4.2 days for children aged less than two years. For hospital discharges which included an ICU stay, the average length of stay in hospital was 10.9 days (to include both days spent in ICU and on other wards) for infants aged less than one year, and 10.8 days for those aged less than two years.

In the case of older adults, data pertaining to discharges from 2013 to 2017 inclusive were highly suppressed, and deemed not suitable for inclusion in this analysis. Costs related to discharges were provided for the entire adult cohort aged 65 years and older. As they were not further disaggregated by age group, the same costs were used across all immunisation strategies targeting older adults. Data relating to discharges with a primary diagnosis of RSV over the period 2018 to 2022 were used to calculate an average cost per hospital discharge (weighted for discharges with and without an ICU stay) of €11,002 for all adults aged 65 years and older. The cost of a hospital episode which included an ICU stay for those with a primary diagnosis of RSV was €40,982. The average length of a hospital stay was 10.0 days for those aged 65 years and older, and 11.2 days in those aged 75 years and older. For all adults aged 65 years and older, the average length of stay of a hospital episode which included an ICU stay was 17.9 days.

5.2.9 Additional organisational costs related to implementation of an RSV immunisation programme

In addition to costs relating to immunisation procurement and administration, potential costs relating to both the initial launch of any new immunisation strategy,

and operational costs of the day-to-day rollout were considered as part of this analysis.

In Ireland, national childhood and adult immunisation programmes are co-ordinated by the National Immunisation Office (NIO) in the HSE. The NIO is responsible for managing vaccine procurement and distribution, and developing training and communication materials for public and health professionals of all National Immunisation Programmes in line with Department of Health Immunisation Policy.(337)

While precise figures relating to immunisation expenditure were not available, the NIO has indicated that costs related to vaccine procurement typically account for approximately 82.5% of overall annual expenditure, while costs related to cold chain services are estimated to account for approximately 16% of total expenditure, followed by 1.5% of total expenditure associated with communication and education materials.

Costs related to product procurement, and assumptions regarding these have already been outlined. Additional costs are described below.

HSE National Cold Chain Service

In Ireland, vaccines offered as part of the national childhood and adult immunisation programmes may be ordered through the HSE National Cold Chain Service (NCCS), after which they are delivered directly to the primary care vaccination site, and may include GP surgeries, community pharmacies, or Local HSE Offices.(338) These vaccines are stored and delivered under temperature controlled conditions by the NCCS.(338) As previously outlined in Chapter 2, all of the technologies under assessment in this costing analysis are required to be stored between 2°C and 8°C. All strategies therefore require the engagement of NCCS services as part of immunisation roll-out.

Strategies considered as part of this analysis aim to deliver immunisation to sizeable target populations, thus it is reasonable to anticipate that additional storage and distribution capacity need to be considered. Through correspondence with the NIO, it is estimated that costs relating to additional storage and distribution agreements associated with a new immunisation strategy would be approximately €600,000.

Aside from additional storage costs, it is anticipated that there may be a 'pick and pack' cost directly associated with each unit of product stored and packed for delivery by the NCCS per season. Based on private correspondence with the NIO, and assuming uptake estimates considered in the base case analysis, further pick

and pack cold chain costs estimated for each eligible population included in this costing analysis are outlined in Table 5.6.

Table 5.6 Additional cold chain costs associated with volume of products processed in base-case analyses considered^

Strategy	Eligible cohort (n)	Uptake (as assumed in base-case analysis) (%)	Additional costs, with VAT 23% (€)
Passive immunisation strategies for protection of children against RSV			
Seasonal immunisation strategy	27,807	88	41,837
Seasonal and catch-up immunisation strategy	55,678	88	83,770
Hybrid immunisation strategy	33,140	88	49,860
Maternal immunisation strategy	27,433	62	29,079
Infants <1 year eligible for palivizumab	240	100	410
Children <2 years eligible for palivizumab	581	100	993
Active immunisation strategies for adults aged 65 years and older against RSV			
Older adults aged ≥65 years	840,830	76	1,092,551
Older adults aged ≥75 years	381,856	87	567,988

Key: n – number; RSV – respiratory syncytial virus; VAT – value-added tax.
^These cold chain costs represent 'pick and pack' costs. They are estimated per unit processed, and are considered as part of the estimated cost of the various strategies. Costs relating to additional storage and distribution requirements which may be placed on the NCCS if an RSV immunisation programme is implemented are considered fixed, and part of overall programme implementation cost.

At present, the NCCS delivery system operates on a fortnightly delivery schedule. Through correspondence with the NIO, it was suggested that introduction of any of the modelled RSV immunisation strategies would not result in a change in this schedule for existing designated sites, and as such no additional delivery costs would accrue. However, a key assumption made as part of this costing analysis was that nirsevimab may be offered to infants born during the RSV season in the days after birth, during the period while they are an inpatient in a maternity hospital and or unit. At present, there are 19 maternity hospitals and or units in Ireland.[339] It was unclear whether all maternity units and or hospitals are currently listed as designated cold chain delivery sites. There may be an increased cost associated with the addition of any new cold chain delivery sites to the NCSS delivery schedule. Likewise, if an infant is to be offered immunisation in the days following birth by a public health nurse, the product will need to be available in the corresponding Local Health Office (LHO), a proportion of which may not be currently listed as cold chain sites. While acknowledging that additional costs associated with the logistics and delivery to a newly designated cold chain delivery site would likely accrue, the scale of these costs are unknown, although they are likely to be small relative to the overall cost of implementing an immunisation programme.

Public health information campaign

The NIO is responsible for developing training and information materials for the public related to national immunisation programmes,[337] in addition to the provision of publications and guidelines for healthcare professionals.[340]

The purpose of these information materials is to inform stakeholders, increase awareness of immunisations being offered to target populations, and increase uptake. Communications and information for healthcare professionals could take the form of direct correspondence, and may target those authorised to administer immunisations (including GPs, community pharmacists and staff nurses), in addition to other healthcare professionals and organisations that promote immunisation campaigns and act as a source of information for older adults and parents of infants eligible for vaccination. Information leaflets targeting both paediatric and adult groups could be funded, and in the case of immunisation strategies targeting infants, could potentially be included as part of antenatal information packs currently provided to pregnant women. Additionally, a digital and media campaign may be carried out, both to raise awareness of any new RSV programme, and to encourage immunisation uptake. The NIO has estimated that communication and information costs associated with the addition of a new product to the childhood immunisation schedule to be approximately €500,000.

Training

In order to administer any vaccine, healthcare professionals are required to meet specific training requirements, which include training in the general parenteral administration of medicinal products, training in administration of cardiopulmonary resuscitation (CPR) for adults and children, and additionally in the case of pharmacists, training with regard to responding to an emergency situation and management of anaphylaxis (or RESMA).[341] As primary care contractors who currently provide vaccination services are already engaging in this training, no additional costs or organisational challenges associated with this training would be anticipated with the introduction of an RSV immunisation programme.

Training programmes for specific vaccines may also be completed before a vaccinator can administer a product (for example, there are specific training programmes which can be completed before administering the following vaccines: seasonal influenza, COVID-19, pneumococcal polysaccharide, and herpes zoster). These training programmes are typically completed online as e-learning modules, and take approximately two hours to complete.[342] No such training programmes specific to immunisation against RSV exist currently in Ireland. Enrolment in the training programme is free of charge for registered individuals. While attendance at the training programme represents an opportunity cost for the vaccine contractor, no additional fees apply. However, there is a cost for the development of the

training programme. The NIO has estimated this to be €50,000 for a novel national immunisation programme.

It should also be considered that, where immunisation takes place in a maternity unit and or hospital, specific training would be required for midwives tasked with nirsevimab administration. This training would encompass education in relation to communication with parents regarding immunisation with nirsevimab, administration of nirsevimab, management of adverse events (such as anaphylaxis), and training in any record-keeping required as part of an RSV immunisation programme. The time requirement is likely similar to that required for vaccine contractors in primary care attending online courses for specific vaccines (that is, approximately two hours). There would be an opportunity cost associated with this training which would be dependent on the number of staff selected to administer nirsevimab as part of any programme. The training would also need to be conducted in the weeks prior to the commencement of an RSV season, which would place additional unquantifiable costs on the HSE if locum and or agency staff were required to provide staff cover while this training was underway.

Programme management

Details of vaccinations administered to both children and adults must be recorded by the vaccinator.[343] These records must be retained locally at the site of vaccine administration, such as at a GP practice, HSE Local Health Office, pharmacy, travel health clinic or occupational clinic, and a patient may request records of vaccination directly from these sites.[343] The NIO also publishes an 'Immunisation Passport', a paper-based booklet which is typically issued at an infant's first routine primary childhood vaccination appointment, and where records of any vaccinations received throughout the life course may be recorded.[344] While there is no national database that stores details of all immunisation records in Ireland,[343] records regarding the administration of COVID-19, influenza and pneumococcal vaccinations by primary care providers are recorded through online portals such as GPVax and PharmaVax.[229, 345, 346] These systems link with the HSE's vaccination platform software system, CoVax, a system used to manage, monitor and support the process of administering these vaccinations across Ireland.[229] In the case of primary childhood immunisations, GPs are required to send complete immunisation records to their corresponding HSE Local Health Office, where these records are entered manually into a regionalised immunisation system. The NIO estimate that the cost of updating IT or data systems to accommodate the addition of a new vaccine to the immunisation schedule may amount to €1 million.

If IT systems are not updated prior to the implementation of an RSV immunisation programme, local paper-based records would be required, with a summary of patient

records sent to relevant bodies (such as NIO or HPSC) to ensure a complete immunisation record for patients. This may be more onerous and labour-intensive than directly inputting patient details into an IT system specifically tailored for an RSV immunisation programme, and there would be hidden unquantifiable costs associated with the extra time that such data management might require, both on the part of the vaccinator, and on the part of the NIO or data collector, collating the information.

Regardless of whether IT-based or paper-based data recording systems are used, it is anticipated that, at a minimum, data would be recorded pertaining to:[344]

- personal details of the adult or child to whom immunisation is administered, such as name, date of birth, address, contact details (or those of the consenting parent/guardian in the case of an infant), personal public service number (PPSN), individual health identifier (IHI), and age of the individual on the day that immunisation is given
- details relating to any medical contra-indications, or previous allergic reactions experienced by the individual, and contact information for the individual's next-of-kin in the event of an emergency
- details of the individual's registered GP, and details of the vaccinator or administrator, such as name, address, and professional registration number
- details of the immunisation product administered, such as the product name, manufacturer, batch number, expiry date, route and site of administration, and the date of administration.

A further cost which may need to be considered when launching a new immunisation strategy includes hiring a national programme manager or programme director by the NIO to oversee implementation and operation of the immunisation programme. This cost was estimated as €119,275 based on HSE Consolidated Salary Scales 2024 for a Grade VIII clerical officer,[347] adjusted for pension, PRSI and overheads in accordance with national guidelines.[305] It should be considered that a programme manager may need to be in place for a period of time prior to roll-out, and throughout the duration, of the immunisation programme.

Where immunisation of infants born during an RSV season would take place in a maternity unit and or hospital, it is likely that one staff member in each hospital would be made responsible for programme implementation and organisation within that setting. For the analysis, it was assumed that an in-hospital programme lead would be assigned responsibility for immunisation roll-out for the duration of the RSV season. The costs associated with local roll-out and nirsevimab administration are considered in section 5.2.10.

5.2.10 Labour costs and considerations

Passive immunisation of infants against RSV

As noted, an assumption of the costing analysis is that infants born during an RSV season will be offered immunisation in the days after birth, either (i) during the clinical assessment routinely conducted on the second day of life in a maternity unit and or hospital setting, or (ii) at the same visit for which the infant is offered newborn bloodspot screening, also known as the heel-prick test.[348] Newborn bloodspot screening is offered as part of routine postnatal care for infants after birth through the National Healthy Childhood Programme (NHCP), and is available to all infants born in Ireland.[306] As previously outlined, this sample is taken in the days after birth, with over 95% of samples taken 72 to 120 hours after birth (in the years 2020, 2021 and 2022).[306] The test may be carried out by a midwife if the infant remains as an inpatient in a maternity hospital or unit, or by a public health nurse (PHN) where an infant has been discharged home.[349] Procedures already exist whereby, if newborn bloodspot screening does not take place in a maternity hospital and or unit, then that hospital and or unit is responsible for notifying the relevant designated LHO PHN service that screening is required after discharge.[350] It may be feasible to operate a similar notification system in the case of a seasonal immunisation programme (using nirsevimab) targeting infants. While it might be possible to leverage off such a referral system, offering immunisation against RSV in two different settings will inevitably pose more logistical challenges. Offering immunisation against RSV alongside other health checks, such as the newborn hearing screening test,[306] while the infant remains an inpatient in the maternity hospital and or unit would remove the need to notify LHOs regarding any necessary follow-up, reduce logistical challenges associated with administration in a second setting, and minimise potential loss of uptake due to incomplete referral or follow-up. In the case of immunisation of infants born outside of the RSV season (and entering their first RSV season), it has been proposed that immunisation with nirsevimab will be offered in through primary care GP practices. In this instance, an administration fee would be payable to the contractor, and as such, it is assumed that no labour cost is associated with immunisation delivery through primary care.

In terms of labour costs, it is reasonable to assume that the healthcare professional will require time to discuss and explain the form of immunisation being provided, and counselling prior to administration. After administration, details of immunisation must be recorded, appropriate paperwork completed and data accurately logged onto an IT system. Manufacturers note that serious hypersensitivity reactions, including anaphylaxis, have been observed with monoclonal antibodies,[8] and due to this risk of anaphylaxis, time must be allowed for post-immunisation observation. No

recommendation could be found to inform the best-practice observation period specifically for nirsevimab or for any other monoclonal antibody. National Immunisation Guidelines for Ireland advise that, in the case of vaccine administration, vaccine recipients should be observed for at least 15 minutes post-vaccination, and where a specific concern about a possible vaccine allergy exists, the recipient should be observed for 30 minutes.[351] Observation of the infants eligible for the catch-up strategy is already required for 15 minutes post-administration of their national primary childhood immunisations.

In the base-case analyses, it was assumed that immunisation against RSV may take an additional 15 minutes of a healthcare professional's time. While staff cost might be considered an opportunity cost, recruitment may be necessary to ensure that delivery of the RSV immunisation programme does not adversely impact the delivery of other services. The cost to the HSE of having a staff nurse or midwife administer nirsevimab to an infant while they are an inpatient in the days after birth is estimated to be €9.26 per dose delivered. The cost to the HSE of having a PHN administer nirsevimab to an infant in the community setting, after inpatient discharge, is estimated to be €12.87 per dose delivered. These figures were estimated using the HSE's Consolidated Salary Scales 2024.[347] No data exist to inform the proportion of newborn bloodspot screening tests which take place as an outpatient or inpatient. It was assumed in the base-case analyses that all infants born during the RSV season will be offered immunisation by a staff midwife in a hospital setting in the days after birth.

A further organisational consideration is the seasonal burden associated with the time required to immunise infants born during the RSV season in an inpatient setting. At present, there are 19 maternity units and or hospitals in Ireland, which differ not only in terms of existing capacity and staff levels, but also in the distribution of births recorded annually. The most recently published data from the National Perinatal Reporting System (NPRS) report that, in 2021, the percentage of all recorded births attributed to a single maternity unit ranged from 1.6% (n=947) to 15.1% (n=9,148).[352] Based on the distribution of total births across the 19 maternity units for 2021, and assuming that immunisation of an infant will require an additional 15 minutes of a staff time, the estimated labour hours required per week per maternity unit between September 2025 and February 2026 for administration of nirsevimab are indicated in Table 5.7 below.

Table 5.7 Estimated additional labour hours required per week for immunisation of infants born during the 2025-2026 RSV season (September – February)

Births reported in a maternity unit per annum (n)	Maternity units (n)	% of total births*	N. of labour hours per week (September - February) per maternity unit required for immunisation of infants~
Less than 1,000	1	1.6	4
1,000-1,999	11	28.3	7
2,000-2,999	1	4.8	13
3,000-3,999	1	5	13
4,000-4,999	1	7.1	19
7,000-7,999	3	38.1	34
8,000 and over	1	15.1	41

Key: n – number
*Percentage of total births was taken from most recently available National Perinatal Reporting System (2021).[352]
~Relates to the number of additional labour hours per week which may be anticipated based on the estimated birth cohort over the period September 2025 to February 2026, assumed in this analysis as 27,807 infants.

As part of this assessment, it was assumed that GPs would receive an administration fee for the immunisation of infants with nirsevimab as part of any catch-up programme offered in the various strategies, and for pregnant women availing of the maternal vaccination strategy. As such, no additional labour costs were considered for these cohorts.

Active immunisation of adults aged 65 years and older against RSV

In the case of adults aged 65 years and older, it is proposed that RSV vaccines will be offered at the start of the RSV season in primary care, as is the case for other seasonal respiratory vaccinations such as COVID-19 and seasonal influenza. As outlined in section 5.2.8, it was assumed that GPs and pharmacists would receive an administration fee for administering the vaccine to this cohort. For simplicity, this same cost was applied to vaccine administration by HSE Vaccination Teams to residents of long-term care facilities (LTCFs). As such, no additional labour costs were considered for adults aged 65 years and older. While recognising that costs in the LTCF setting may differ and that an administration fee would not be paid as vaccination would be undertaken by HSE staff, this cohort represent a minority of all potential eligible individuals.

It should be noted that COVID-19, seasonal influenza and RSV vaccines are all administered by intramuscular injection via the deltoid muscle. As outlined in Chapter 2 (section 2.5.3), both RSVpreF and RSVPreF3 may be administered concurrently with specified seasonal influenza vaccines; however, no data yet exist to inform co-administration with COVID-19 vaccines. Therefore, at present it may not be possible for a GP to administer all three seasonal respiratory vaccines (against COVID-19, influenza and RSV) to an individual in the same visit. Moreover, while a GP is authorised to administer up to three injections via the deltoid muscle at a single visit, a pharmacist administering vaccines in primary care is limited to administering up to two vaccines only (that is, one vaccine per deltoid muscle). As such, it would not be possible for a pharmacist to administer all three seasonal respiratory vaccines in the same visit. This would not have additional cost implications from a payer perspective where vaccines are delivered in primary care, as an administration fee for each vaccine will likely be payable to the vaccinator regardless of the timing of administration, but it is an organisational consideration that needs to be noted, and one that may impact uptake in this cohort. Similarly, for HSE Vaccination Teams that currently go to LTCFs to offer vaccination against COVID-19 and seasonal influenza to eligible residents, it may not be possible administer all three seasonal respiratory vaccines to an individual in the same visit. This may necessitate an additional visit to each facility, which may present an organisational challenge.

5.2.11 Summary of assumptions and handling of uncertainty for costing analysis

The potential impact on healthcare utilisation and health outcomes of introducing a novel immunisation strategy for any of the eligible populations is subject to considerable uncertainty. The technologies under assessment have only recently received market authorisation, and real-world evidence of their effectiveness against RSV is currently limited, though it is anticipated that more evidence may become available related to the 2023-2024 RSV season. As outlined in section 5.2.8, the unit costs of any new technology under consideration may differ from that assumed in the base-case analyses, and as such, estimates considering a range of product unit costs are presented in the scenario analyses to reflect this uncertainty. Coverage is difficult to anticipate, particularly in the case of the immunoprophylaxis of infants against RSV with nirsevimab; the acceptability of a monoclonal antibody to the general population is unknown, though uptake may be bolstered by the experience from national pilots in France and Spain and the evidence of the low risk of adverse events associated with nirsevimab. To reflect the uncertainty in uptake of the maternal vaccine, anticipated health outcomes at varying uptake levels (range: 42%

to 62%) are also presented, to provide an indication of the range of outcomes that could be avoided.

Data obtained from HPSC and HIPE indicate a trend for increasing incidence of notified RSV cases in infants post-COVID-19, particularly since 2021. It is not known if this is a consequence of increased testing or increased transmission and viral circulation. As such, a binomial linear model was used to estimate predicted annual values for the 2024-2025 RSV season for all infant populations in this analysis, based on these trends. Similarly for older adults, a marked increase was observed in the notified cases of RSV in 2022 and 2023, and in hospital discharges for 2022 (2023 data not yet available). To reflect this higher incidence, the most recent available data from 2022 was used to inform the estimates used in the costing analysis for the older adult population. As outlined in Chapter 3, the technologies under assessment have shown favourable safety profiles in clinical trials. In this costing analysis, it was assumed that any harm resulting from administration of the technologies assessed was minimal, and consequently, no costs associated with such harms were considered.

It should be noted that palivizumab is only partially funded by the HSE in Ireland. Where an infant child is eligible for a General Medical Services (GMS) card, a prescription charge does not apply to High Tech Medicines and, as such, palivizumab may be obtained free of charge on foot of a prescription.[353] Where an infant child is not eligible for a GMS card, palivizumab may be accessed through the Drug Payment Scheme (DPS), where a co-payment of up to €80 is paid per family per month for drugs received in the community.[354] As such, where an infant child is not eligible for a GMS card, within this context, a typical course of five monthly doses may amount to a cost to the parent or guardian of €400. Of note, the co-payment of €80 is applied at the level of the family and reflects a maximum monthly payment for all eligible prescription items; for some infants and or their families who are regularly on other prescription items, this co-payment may not represent an additional charge. However, owing to the substantial cumulative cost of this co-payment, and considering the monthly administration schedule, it should be considered that there may be some children who are eligible for palivizumab, but whose parents have opted not to avail of this treatment. To account for this uncertainty, scenario analyses were conducted considering an increase in these at-risk infant populations of 5% and 10%.

Costing a range of combination strategies was considered beyond the scope of this analysis. However, should a maternal immunisation strategy be adopted, there will be a cohort of infants who will not be protected for the RSV season. Such instances include where a mother does not opt to avail of the maternal vaccine during

pregnancy, where an infant is born within two weeks of the mother receiving the maternal vaccine, or where the infant is born prior to the third trimester (and so adequate antibody transfer may not yet have occurred).[11] The option is to provide immunoprophylaxis with a monoclonal antibody (either palivizumab, if appropriate, or nirsevimab) after birth for these infants. For infants due to be born during the RSV season (seasonal infant cohort), a scenario analysis was conducted to estimate potential upper and lower bounds of expenditure associated with offering a combination strategy, considering both maternal immunisation at varying vaccine uptake rates (30% and 60%), and offering nirsevimab to the those not protected by maternal immunisation.

In Chapter 3 of this report, available evidence of the clinical effectiveness and safety of agents which provide immunoprophylaxis against RSV, which underpinned countries' recommendations, has been outlined (sections 3.3.3 and 3.4.2). The risk of serious adverse events in those receiving immunisation was deemed minimal. Consequently, there were no costs associated with adverse events which may occur as after administration of any of the products proposed in the strategies modelled in this analysis (that is, nirsevimab, RSVpreF, and RSVPreF3).

As outlined in section 5.2.8, there would be over-arching costs associated with the implementation and organisation of a novel RSV immunisation programme. While these costs are anticipated irrespective of immunisation uptake, or size of the target population, it was assumed that they would not apply if a decision was taken not to offer immunisation to older adults or to the general infant population. That is, it was assumed that there would be no programme-level costs if a decision was limited to offering nirsevimab to those children who are currently eligible to receive palivizumab.

To handle uncertainty which exists across the aforementioned parameters, a probabilistic sensitivity analysis was undertaken to inform the base-case results. A deterministic one-way sensitivity analysis (OWSA) was also undertaken, to identify parameters to which the base case for the total cost in each strategy is most sensitive. Product unit costs were varied 20% above and below their assumed base-case price, as were all administration fees and labour costs associated with immunisation delivery. Results of the OWSA conducted are presented as tornado plots. All parameter values considered in the base-case analyses have been outlined earlier in this chapter; however, parameter values and confidence intervals considered for each strategy as part of the sensitivity analysis can be seen in Appendix 5A.

5.2.12 Quality assurance

The costing analysis was developed in accordance with national HTA guidelines, and quality assured in accordance with the HTA quality assurance framework. All model inputs and outputs were reviewed by a second member of the evaluation team.

5.3 Results

The results of this costing analysis are detailed below, starting with a summary of the base-case results (section 5.3.1). This is followed by scenario analyses which provide estimates of the mean costs for each strategy (sections 5.3.2). Finally, a OWSA is presented for each strategy (section 5.3.3).

5.3.1 Summary of base-case results

Immunisation of children at increased risk of severe lower respiratory tract disease associated with RSV

Table 5.8 presents the estimated one-year incremental costs associated with the passive immunisation of children (who are at increased risk of severe LTRD associated with RSV) with nirsevimab instead of palivizumab, considering the previously outlined base-case assumptions. A switch to a strategy of nirsevimab administration for infants aged less than one year, or children aged less than two years, would cost less than current care. The cost reductions for these strategies were estimated at €0.85 million (-€1.24 million to -€0.52 million) and €2.07 million (-€2.94 million to -€1.35 million), respectively. As the analysis assumes that nirsevimab has the same efficacy as palivizumab in this cohort, no change to health outcomes are anticipated with this switch.

Table 5.8 One year incremental costs associated with the passive immunisation of children (at increased risk of severe RSV-associated lower respiratory tract disease) with nirsevimab instead of palivizumab

Strategy	Eligible population	Uptake (%)	Expenditure relating to product procurement, NCCS costs and administration fees (95% CI) (€ million)
Infants aged less than one year and eligible for palivizumab	240	100	-0.85 (-1.24 to -0.52)
Children aged less than two years and eligible for palivizumab	581	100	-2.07 (-2.94 to -1.35)

Key: NCCS – National Cold Chain Service; RSV – respiratory syncytial virus.
Note: In the absence of evidence, it was assumed that the clinical effectiveness was the same for palivizumab and nirsevimab.

Programme implementation costs

As outlined in sections 5.2.9 and 5.2.10, there are implementation costs which would likely apply with the introduction of any new RSV programme for the general infant population or for older adults. These costs would likely apply irrespective of the target population(s) considered, and would not vary with immunisation uptake. These fixed costs are summarised in Table 5.9 below.

Table 5.9 Estimated costs associated with the implementation of any novel RSV immunisation programme

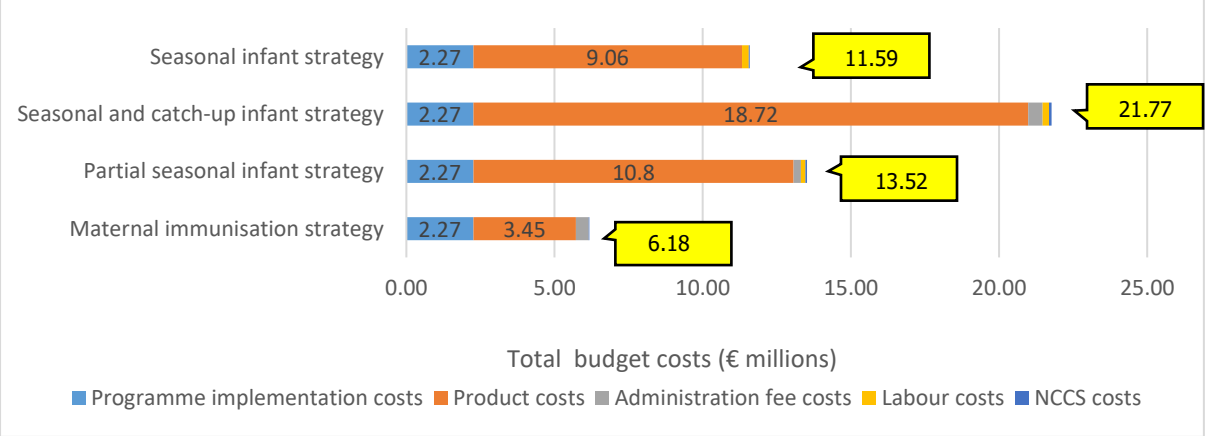
Additional organisational costs	€
NCCS costs relating to storage and distribution~	600,000
Information campaign	500,000
Training	50,000
National Programme Manager	119,275
IT systems update	1,000,000
Total	2,269,275

Key: IT – information technology; NCCS – National Cold Chain Service.
~Estimated NCCS costs above relate to additional storage and distribution requirements which may be placed on the NCCS, and are assumed fixed. In addition to these fixed costs, an additional NCCS cost per unit processed is payable by the HSE, and these are estimated accordingly for each strategy.

Strategies involving the passive immunisation of infants against RSV (general infant population)

Figure 5.2 provides a breakdown of the total costs associated with the implementation of a one-year immunisation programme for strategies targeting the general infant populations, including both fixed and variable costs. It outlines the proportion of costs associated with implementation of a new national programme (fixed cost as previously outlined in Table 5.9), product procurement, relevant administration fees payable and or labour costs, and associated NCCS costs. Product costs are consistently the largest proportional cost associated with these strategies, followed by programme implementation costs, and additional cold chain storage.

Figure 5.2 Breakdown of the total one-year costs associated with passive immunisation of the general infant population



~Programme implementation costs include those as outlined in Table 5.9, which would be applicable in the case of any novel RSV immunisation programme, and do not vary with the size of the target population considered, or with immunisation uptake.

Table 5.10 provides a summary of outcomes that could be avoided in the general infant population associated with various immunisation strategies. These assume an uptake rate of 88% for nirsevimab-based strategies and an uptake of 66% for the maternal immunisation strategy.

The strategy associated with the greatest benefit is the seasonal plus catch-up strategy. It is estimated that a mean of 1,679 (95% CI: 1,365 to 1,996) notified cases of RSV would be avoided with this strategy. Among those with a primary diagnosis of RSV, it is estimated that a mean of 1,393 (95% CI: 1,078 to 1,718) RSV-associated hospital discharges, 129 (95% CI: 91 to 174) of which include an ICU stay, would be avoided. Accordingly, it is estimated that a mean of €13.55 million (95% CI: €10.16 million to €17.23 million) in hospital costs may be averted, through an estimated 5,973 (95% CI: 4,255 to 7,931) hospital bed days averted, 1,404 (95% CI: 844 to 2,132) of which relate to bed days which include an ICU stay. However, it is noted that this is also the strategy with the largest number of infants protected as it considers the immunisation of all infants aged less than one year in their first RSV season (n=55,678) and a nirsevimab uptake rate of 88%.

The strategy associated with the lowest benefit is the maternal immunisation strategy. It is estimated that a mean of 532 (95% CI: 336 to 694) RSV cases would be avoided, and in those with a primary diagnosis of RSV, it would avoid a mean of 406 (95% CI: 194 to 577) RSV-associated hospital discharges, 38 (95% CI: 17 to 57) of which include an ICU stay. An estimated €3.95 million (95% CI: €1.88 million to €5.77 million) in hospital costs could be averted through 1,739 (95% CI: 812 to 2,631) hospital bed days avoided, 408 (95% CI: 173 to 684) of which relate to a hospital discharge which include an ICU stay. Notably however, it is also the strategy

that is associated with the smallest number of infants protected (n=27,433 women eligible for immunisation with a lower uptake rate (62%) compared with the nirsevimab-based strategies (88%)). As outlined in section 5.2.7, RCT data also indicate that maternal immunisation (VE: 70.9% (95% CI: 44.5% to 85.9%)) is less effective than passive immunisation with nirsevimab (VE: 80% (95% CI: 70% to 87%)).

Table 5.10 Summary of health outcomes that could be avoided in the general infant population associated with various immunisation strategies

	Seasonal immunisation strategy	Seasonal and 'catch-up' immunisation strategy	Hybrid immunisation strategy	Maternal immunisation
Eligible population (n)	27,807	55,678	33,140	27,433
Uptake (%)	88			62
Mean number of notified RSV cases avoided (n) (95% CI)	838 (684 to 997)	1,679 (1,365 to 1,996)	999 (811 to 1,194)	532 (336 to 694)
Mean number of RSV-related (n)				
Hospital discharges avoided (95% CI)	696 (536 to 863)	1,393 (1,078 to 1,718)	829 (639 to 1,025)	406 (194 to 577)
Hospital discharges which include an intensive care unit stay avoided (95% CI)	65 (45 to 87)	129 (91 to 174)	77 (54 to 103)	38 (17 to 57)
Deaths avoided (95% CI)	0 (0 to 1)	0 (0 to 3)	0 (0 to 2)	0 (0 to 0)
Hospital bed days avoided (95% CI)	2,992 (2,134 to 4,006)	5,973 (4,255 to 7,931)	3,554 (2,520 to 4,755)	1,739 (812 to 2,631)
Hospital bed days which included an intensive care unit stay avoided (95% CI)	700 (422 to 1,071)	1,404 (844 to 2,132)	835 (500 to 1,281)	408 (173 to 684)
Mean RSV-related hospital costs avoided (95% CI) (€ million)	6.78 (5.06 to 8.63)	13.55 (10.16 to 17.23)	8.08 (6.06 to 10.31)	3.95 (1.88 to 5.77)

Key: CI – confidence intervals; n – number; RSV – respiratory syncytial virus.

Table 5.11 presents the estimated incremental costs which may be associated with the passive immunisation of infants in the general population, considering the

previously outlined base-case assumptions. These estimates exclude the fixed costs associated with the implementation of any novel RSV immunisation programme as outlined in Table 5.9.

At the assumed base-case cost of nirsevimab (€301.12 per unit), the incremental cost of extending an RSV immunisation programme with nirsevimab to include infants in the general population was estimated to range from €2.54 million (95% CI: -1.17 million to €6.80 million) for the seasonal immunisation strategy to €5.45 million (95% CI: €-1.96 million to €13.97 million) for the seasonal and catch-up immunisation strategy. While there is considerable uncertainty around all estimates, the model indicates that all immunisation strategies with nirsevimab would result in cost offsets associated with a reduction in RSV-related hospital discharges (ranging from €6.78 million (95% CI: €5.06 million to €8.63 million) in the case of the seasonal immunisation strategy, to €13.55 million (95% CI: €10.16 million to €17.23 million) in the case of the seasonal and catch-up immunisation strategy). At the assumed base-case price, the cost associated with each of the nirsevimab strategies is approximately 1.5 times higher than the estimated RSV-related hospital costs averted.

It was estimated that RSV-related hospital costs averted due to a maternal immunisation strategy would be roughly equivalent to the variable costs associated with delivering the strategy. That is, given the assumptions of the base case, a maternal immunisation strategy would potentially be budget-neutral relative to current care (cost €0.01 million, 95% CI: -€2.24 million to €2.43 million). As noted, the cost per immunised child is lower compared with nirsevimab-based strategies given the lower unit cost per dose of the vaccine. Moreover, this strategy considers an uptake of only 62% in the maternal population (compared with 88% in the nirsevimab strategies), and therefore the potential population that is protected is smaller. Accordingly, potential cost offsets associated with a reduction in RSV-related hospital discharges are lower (€3.95 million, 95% CI: €1.88 million to €5.77 million) compared with the other strategies considered.

Table 5.11 One-year incremental costs for strategies involving the passive immunisation of infants – base-case analysis

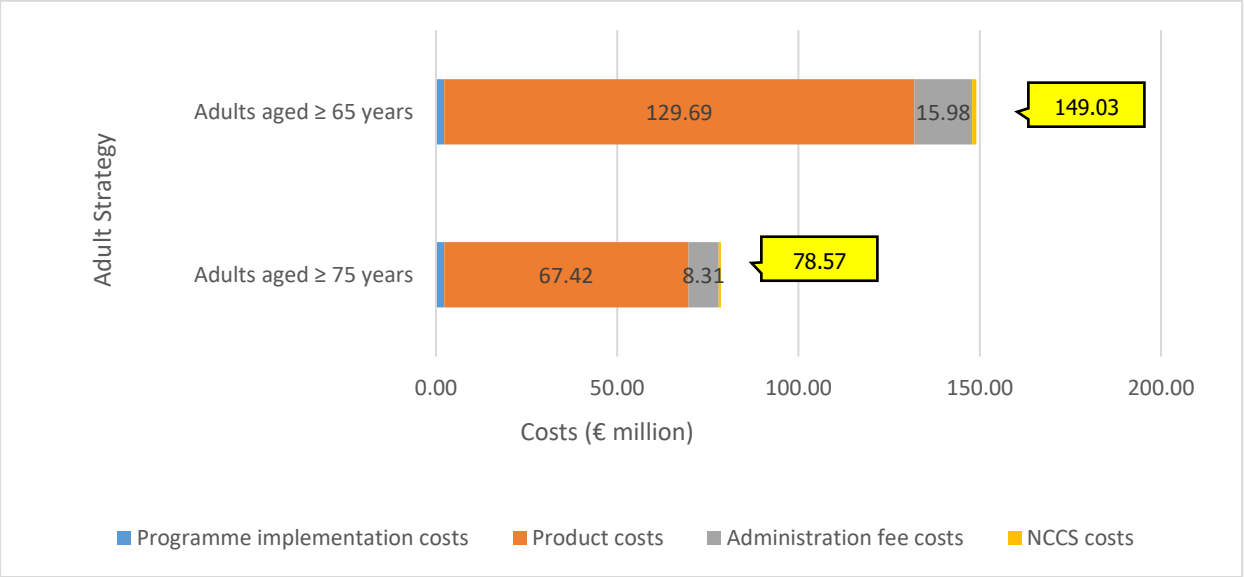
Strategy	Eligible population	Uptake (%)	Expenditure relating to product procurement, NCCS costs* and administration fees (95% CI) (€ million)	Additional labour costs (95% CI) (€ million)	RSV-related hospital costs avoided (95% CI) (€ million)	Incremental costs (95% CI) (€ million)
Seasonal immunisation strategy	27,807	88	9.10 (5.90 to 12.90)	0.22 (0.14 to 0.32)	6.78 (5.06 to 8.63)	2.54 (-1.17 to 6.80)
Seasonal and catch-up immunisation strategy	55,678	88	18.77 (12.39 to 26.58)	0.22 (0.14 to 0.32)	13.55 (10.16 to 17.23)	5.45 (-1.96 to 13.97)
Hybrid immunisation strategy	33,140	88	11.10 (7.30 to 15.79)	0.15 (0.10 to 0.22)	8.08 (6.06 to 10.31)	3.16 (-1.24 to 8.21)
Maternal immunisation strategy	27,433	62	3.93 (2.69 to 5.42)	NA	3.95 (1.88 to 5.77)	-0.01 (-2.24 to 2.43)

Key: CI – confidence interval; NCCS – National Cold Chain Service; RSV – respiratory syncytial virus
Note: Costs exclude the fixed costs associated with the implementing a new national programme.
*NCCS costs relate specifically to volume of products processed by NCCS as part of these strategies.

Strategies involving active immunisation of older adults

Figure 5.3 provides a breakdown of the total cost of implementing each immunisation strategy targeting adults aged 65 years and older, and aged 75 years and older considering both the fixed cost of implementing a novel RSV programme and variable costs. As the analysis assumes that the cost of both RSVpreF and RSVPreF3 to be the same, the total one-year costs are the same for each of these comparisons. The figure shows the proportion of costs associated with programme implementation (fixed cost), product procurement, administration fees payable and associated NCCS costs (per unit processed). It highlights that the main driver for each strategy is the cost of the vaccine.

Figure 5.3 Breakdown of the total one-year costs associated with alternative immunisation strategies for older adults



~Programme implementation costs include those as outlined in Table 5.9, which would be applicable in the case of any novel RSV immunisation programme, and do not vary with the size of the target population considered, or with the uptake.

Table 5.12 provides a summary of outcomes that could be avoided in the older adult population associated with various immunisation strategies. A strategy based on providing RSVpreF to all adults aged 65 years and older was associated with the greatest benefit. It was estimated that a mean of 1,074 (95% CI: 726 to 1,303) notified cases of RSV would be avoided with this strategy. Among those with a primary diagnosis of RSV, it is estimated that a mean of 108 (95% CI: 70 to 138) RSV-associated hospital discharges, 8 (95% CI: 3 to 14) of which include an ICU stay, and 1 (95% CI: 0 to 1) death would be avoided. Accordingly, it is estimated that €1.18 million (95% CI: €0.70 million to €1.71 million) in RSV-related hospital costs would be avoided though an estimated 1,071 (95% CI: 651 to 1,508) RSV-

related hospital bed days averted, 143 (95% CI: 58 to 267) of which include an ICU stay. However, it is also the strategy with the largest number of individuals protected as it considers offering immunisation to all adults aged 65 years and older (n=840,830) and a vaccine uptake rate of 76%. While the same number of individuals are assumed to be immunised in a strategy based on the RSVPreF3 vaccine, the associated health benefits are slightly lower given the assumption of lower vaccine effectiveness based on RCT data (82.6% [96.95% CI: 57.9% to 94.1%] vs. 88.9% [95% CI: 53.6% to 98.7%]).

If immunisation is limited to the cohort of individuals aged 75 years and older, fewer health benefits would accrue; however, the reduction is disproportional relative to the reduction in the number of individuals immunised. For example, for a strategy based on RSFpreF, there would be approximately 60% fewer individuals immunised (considering the size of the eligible population (381,856 vs. 840,830) and differences in the uptake rate (87% vs 76%)), but the strategy would still accrue approximately 80% of the mean number of hospital discharges avoided (88 [95% CI: 55 to 115] vs. 108 [95% CI: 70 to 138]) and 92% of the RSV-related bed days avoided (985 [95% CI: 523 to 1,532] vs. 1,071 [95% CI:651 to 1,508]).

Table 5.12 Summary of health outcomes that could be avoided in older adults associated with various immunisation strategies

	Adults ≥65 years		Adults ≥75 years	
Vaccine	RSVpreF	RSVPreF3	RSVpreF	RSVPreF3
Eligible population (n)	840,830	840,830	381,856	381,856
Uptake (%)	76		87	
Mean number of notified RSV cases avoided (n) (95% CI)	1,074 (726 to 1,303)	997 (696 to 1,227)	859 (561 to 1,020)	797 (564 to 960)
Mean number of RSV-related (n):				
Hospital discharges avoided (95% CI)	108 (70 to 138)	100 (68 to 129)	88 (55 to 115)	82 (55 to 107)
Hospital discharges which include an intensive care unit stay avoided (95% CI)	8 (3 to 14)	7 (3 to 13)	7 (2 to 13)	6 (2 to 12)
Deaths avoided (95% CI)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0 (0 to 1)
Hospital bed days avoided (95% CI)	1,071 (651 to 1,508)	993 (627 to 1,400)	985 (523 to 1,532)	910 (504 to 1,414)
Hospital bed days which included an intensive care unit stay avoided (95% CI)	143 (58 to 267)	134 (55 to 251)	118 (39 to 240)	109 (38 to 222)
Mean RSV-related hospital costs avoided (95% CI) (€ million)	1.18 (0.70 to 1.71)	1.10 (0.67 to 1.61)	0.97 (0.55 to 1.42)	0.90 (0.54 to 1.34)

Key: CI – confidence intervals; n – number; RSV – respiratory syncytial virus

Table 5.13 presents the one-year incremental costs associated with alternative immunisation strategies against RSV for older adults for one year, considering the previously outlined base-case assumptions. As before, these estimates exclude the fixed cost associated with implementation of any new immunisation programme.

The incremental cost of immunisation of adults aged 65 years and older (n>840,000) with RSVpreF was estimated to be €144.8 million (95% CI: €98.9 million to €200.5 million). Use of RSVPreF3 instead in this population resulted in a similar, but slightly higher, incremental cost of €144.9 million (95% CI: €99.1 million to €200.5 million). As noted above, the cost of both approaches were the same; however, due to its lower estimated effectiveness, RSVPreF3 was associated with

lower cost offsets (€1.1 million (95% CI: €0.7 million to €1.6 million) vs. €1.2 million (95% CI: €0.7 million to €1.7 million)).

If immunisation is limited to adults aged 75 years and older (n=approximately 382,000), the incremental cost was estimated to be €75.2 million (95% CI: €51.0 million to €104.6 million) for RSVpreF and was slightly higher for a strategy based on RSVPreF3 (€75.2 million [95% CI: €51.1 million to €105.1 million]). Again this was due to a lower cost offsets with the RSVPreF3 strategy (€0.9 million [95% CI: €0.5 million to €1.3 million] vs. €1.0 million [95% CI: €0.6 million to €1.4 million]).

For all strategies considered, the incremental cost was associated with substantial uncertainty as indicated by the wide confidence intervals.

Table 5.13 One-year incremental costs for strategies involving the active immunisation of older adults against RSV – base case

Strategy	Eligible population	Uptake (%)	Expenditure relating to product procurement, NCCS costs* and administration fees (€ million)	RSV-related hospital costs avoided (€ million)	Incremental costs (€ million)
Older adults ≥65 - RSVpreF	840,830	76	146.0 (100.2 to 201.6)	1.2 (0.7-1.7)	144.8 (98.9 to 200.5)
Older adults ≥65 - RSVPreF3	840,830	76	146.0 (100.2 to 201.6)	1.1 (0.7 to 1.6)	144.9 (99.1 to 200.5)
Older adults ≥75 - RSVpreF	381,856	87	76.2 (51.9 to 105.6)	1.0 (0.6 to 1.4)	75.2 (51.0 to 104.6)
Older adults ≥75 - RSVPreF3	381,856	87	76.25 (51.9 to 105.6)	0.9 (0.5 to 1.3)	75.2 (51.1 to 105.1)

Key: NCCS – National Cold Chain Services; RSV – respiratory syncytial virus
Note: Costs exclude the fixed costs associated with the implementing a new national programme.
*NCCS costs relate specifically to volume of products processed by NCCS as part of these strategies.

5.3.2 Scenario analyses

This section outlines results of scenario analyses indicating the potential costs and benefits associated with each immunisation strategy.

Potential costs associated with switching from palivizumab to nirsevimab in those at increased risk of severe RSV disease

Table 5.14 presents the potential incremental costs to the HSE (at varying unit costs of nirsevimab ranging from €209.00 to €393.24 ex VAT) from the scenario analyses. Nirsevimab uptake of 100% is assumed in populations eligible to receive palivizumab (n=240 <1 yr.; n=581<2 years). Labour costs are applied to immunisation of all infants born during an RSV season, where it was assumed that the initial dose would be given in hospital. For all infants born outside of an RSV season, and children entering their second RSV season, it was assumed that nirsevimab may be administered in a primary care setting, in which case an administration fee would be payable to the administering GP. Results reflecting a 5% and 10% increase in the population availing of immunisation for both cohorts are shown, to reflect any increase in uptake which might be expected from the abolition of a co-payment or from the additional convenience associated with a single-dose schedule.

For all populations and unit costs assumed, nirsevimab would cost less compared with the estimated cost of immunising these children with palivizumab. Increases in the size of the eligible population do not result in substantial changes in the estimated mean cost of nirsevimab immunisation, as the overall number of eligible individuals remains low.

Table 5.14 Mean incremental immunisation costs associated with a switch to nirsevimab for children at increased risk of RSV-associated severe disease at varying unit costs and considering different numbers of eligible children

Children (n)	Mean incremental costs of immunisation by switching from palivizumab to nirsevimab at various unit costs (95% CI) (€ in millions)						
	Nirsevimab cost (€209.00 plus 23% VAT)	Nirsevimab cost (€255.06 plus 23% VAT)	Nirsevimab cost (€301.12 plus 23% VAT)	Nirsevimab cost (€347.18 plus 23% VAT)	Nirsevimab cost (€393.24 plus 23% VAT)	Administration fee	Labour costs
Infants aged less than one year at increased risk of severe LRTD associated with RSV							
240	**-0.87 (-1.28 to -0.54)**	**-0.86 (-1.26 to -0.53)**	**-0.84 (-1.25 to -0.52)**	**-0.83 (-1.23 to -0.51)**	**-0.82 (-1.22 to -0.49)**	**0 (0 to 0)**	**0 (0 to 0)**
252	-0.92 (-1.34 to -0.57)	-0.91 (-1.33 to -0.56)	-0.89 (-1.31 to -0.55)	-0.88 (-1.30 to -0.53)	-0.86 (-1.29 to -0.51)	0 (0 to 0)	0 (0 to 0)
264	-0.96 (-1.40 to -0.60)	-0.95 (-1.40 to -0.59)	-0.93 (-1.39 to -0.57)	-0.92 (-1.36 to -0.55)	-0.90 (-1.35 to -0.54)	0 (0 to 0)	0 (0 to 0)

Children (n)	Mean incremental costs of immunisation by switching from palivizumab to nirsevimab at various unit costs (95% CI) (€ in millions)						
	Nirsevimab cost (€209.00 plus 23% VAT)	Nirsevimab cost (€255.06 plus 23% VAT)	Nirsevimab cost (€301.12 plus 23% VAT)	Nirsevimab cost (€347.18 plus 23% VAT)	Nirsevimab cost (€393.24 plus 23% VAT)	Administration fee	Labour costs
Children aged less than two years at increased risk of severe LRTD associated with RSV							
581	**-1.90 (-2.76 to -1.17)**	**-1.86 (-2.72 to -1.14)**	**-1.83 (-2.71 to -1.12)**	**-1.80 (-2.68 to -1.07)**	**-1.76 (-2.66 to -1.01)**	**0.01 (0.01 to 0.01)**	**0.00 (0.00 to 0.00)**
610	-1.99 (-2.91 to -1.23)	-1.95 (-2.86 to -1.20)	-1.92 (-2.84 to -1.14)	-1.88 (-2.81 to -1.13)	-1.85 (-2.78 to -1.09)	0.01 (0.01 to 0.01)	0.00 (0.00 to 0.00)
639	-2.08 (-3.03 to -1.28)	-2.05 (-3.01 to -1.26)	-2.01 (-2.96 to -1.20)	-1.98 (-2.93 to -1.17)	-1.94 (-2.90 to -1.15)	0.01 (0.01 to 0.01)	0.00 (0.00 to 0.00)

Key: CI – confidence interval; LRTD – lower respiratory tract disease; n – number; RSV – respiratory syncytial virus; VAT – value-added tax.
Note: Labour and administration fee costs are associated with these infant and child cohorts as previously outlined. However, owing to the size of the populations considered and due to rounding, where the cumulative associated cost was below €10,000, this appears as zero cost in the table above.

Potential costs associated with extending immunisation with nirsevimab to the general infant population

As a scenario analysis, Table 5.15 presents the potential costs related to procurement and administration fees payable (at varying uptake rates and varying unit costs) to the HSE associated with extending immunisation with nirsevimab to various subgroups in the general infant population who are not currently eligible to receive palivizumab. The base case assumes a unit cost of €301.12 (plus 23% VAT per dose). In the scenario analysis, the ex-VAT unit costs were varied from €209.00 to €393.24, while uptake was varied from by plus or minus 5% (83% and 93% relative to 88% in the base case). Considering the seasonal immunisation strategy for example, compared with the base case which estimates the cost of product procurement to be €9.05 million (95% CI: €5.86 million to €12.86 million), the cost of product procurement at an ex-VAT unit cost of €393.24 and uptake of 93% was estimated at €12.48 million (8.09 to 17.81).

Table 5.15 Mean costs associated with extending immunisation with nirsevimab to the general infant population at varying uptake rates and unit costs

Uptake %	Mean costs of extending immunisation with nirsevimab at various uptake rates and costs (95% CI) (€ in millions)*							
	Nirsevimab cost (€209.00 plus 23% VAT)	Nirsevimab cost (€255.06 plus 23% VAT)	Nirsevimab cost (€301.12 plus 23% VAT)	Nirsevimab cost (€347.18 plus 23% VAT)	Nirsevimab cost (€393.24 plus 23% VAT)	Administration fee	Labour costs	NCCS~ costs
Seasonal immunisation strategy								
83%	5.94 (3.85 to 8.56)	7.27 (4.62 to 10.40)	8.54 (5.53 to 12.13)	9.87 (6.39 to 14.15)	11.14 (7.22 to 15.90)	0	0.21 (0.14 to 0.30)	0.04
88%	6.29 (4.08 to 9.08)	7.71 (4.90 to 11.03)	**9.05 (5.86 to 12.86)**	10.47 (6.77 to 15.00)	11.81 (7.65 to 16.86)	0	0.22 (0.14 to 0.32)	0.04
93%	6.65 (4.31 to 9.60)	8.15 (5.18 to 11.65)	9.57 (6.20 to 13.59)	11.06 (7.16 to 15.85)	12.48 (8.09 to 17.81)	0	0.24 (0.15 to 0.34)	0.04
Seasonal and catch-up immunisation strategy								
83%	11.85 (7.67 to 17.04)	14.51 (9.31 to 20.76)	17.17 (11.15 to 24.52)	19.79 (12.74 to 28.32)	22.27 (14.41 to 31.70)	0.46 (0.30 to 0.65)	0.21 (0.14 to 0.30)	0.08
88%	12.57 (8.13 to 18.06)	15.39 (9.87 to 22.02)	**18.21 (11.82 to 26.00)**	20.98 (13.51 to 30.03)	23.61 (15.27 to 3.61)	0.48 (0.32 to 0.69)	0.22 (0.14 to 0.32)	0.08
93%	13.28 (8.60 to 19.09)	16.26 (10.43 to 23.27)	19.24 (12.49 to 27.48)	22.18 (14.28 to 31.73)	24.95 (16.14 to 35.52)	0.51 (0.33 to 0.73)	0.24 (0.15 to 0.34)	0.09
Hybrid immunisation strategy								
83%	7.07 (4.59 to 10.08)	8.64 (5.63 to 12.27)	10.19 (6.60 to 14.61)	11.73 (7.62 to 16.87)	13.28 (8.59 to 19.01)	0.23 (0.15 to 0.33)	0.14 (0.09 to 0.20)	0.05
88%	7.50 (4.87 to 10.69)	9.16 (5.97 to 13.01)	**10.80 (7.00 to 15.49)**	12.44 (8.08 to 17.89)	14.08 (9.11 to 20.16)	0.25 (0.16 to 0.35)	0.15 (0.10 to 0.22)	0.05
93%	7.93 (5.15 to 11.30)	9.68 (6.31 to 13.75)	11.41 (7.40 to 16.37)	13.15 (8.53 to 18.90)	14.88 (9.63 to 21.30)	0.26 (0.17 to 0.37)	0.16 (0.10 to 0.23)	0.05

Key: CI – confidence intervals; NCCS – National Cold Chain Service; VAT – value-added tax.

*Mean costs exclude fixed costs associated with programme implementation.

~NCCS costs relate specifically to volume of products processed by NCCS as part of these strategies.

Uncertainty associated with the assumed administration fee payable to those delivering immunisation to infants in primary care was reflected through varying the assumed administration fee payable (€19.73) by 20% over and under its mean in the probabilistic sensitivity analyses.

For a seasonal infant and catch-up immunisation strategy, the administration fee payable accounts for 2.56% of total expenditure (considering product administration, administration fees payable, NCCS 'pick and pack' costs, and labour costs) in the base-case analysis. If this administration fee was in fact higher, at €25 per unit delivered, administration fees payable would account for 3.22% of total expenditure. If the administration fee payable was €30 per unit delivered, this figure would rise to 3.84% of total expenditure.

For a hybrid immunisation strategy, the administration fee payable was estimated to account for 2.2% of total expenditure in the base-case analysis. If increased to €25 or €30 per unit delivered, this could increase to 2.78% or 3.31% of total expenditure, respectively.

Potential costs and benefits associated with introducing a maternal immunisation programme for one RSV season

As a scenario analysis, Table 5.16 presents the potential costs of procurement and administration fees payable (at varying uptake rates and varying unit costs) to the HSE associated with introducing a maternal immunisation programme for one RSV season. These estimates use a projected population of 27,433 pregnant women. Assuming a 62% uptake, procurement costs are estimated at €3.47 million (95% CI: €2.25 million to €4.95 million) assuming a unit cost of €165 (plus 23% VAT per dose) compared with €3.07 million (95% CI: €1.99 million to €4.40 million) if the unit cost is €145 (plus 23% VAT per dose).

Table 5.17 provides a summary of outcomes that could be avoided at varying antenatal vaccine uptake rates ranging from 42% to 62%. It can be seen that changes in the uptake rate lead to proportional changes in the health outcomes and hospital costs averted. For example, if uptake in this population is as low as 42%, it was estimated that health outcomes averted could include 361 (95% CI: 228 to 470) RSV cases, 275 (95% CI: 131 to 391) RSV-related hospital discharges, and 25 (95% CI: 12 to 39) RSV-related hospital discharges that included an ICU stay. Hospital costs averted at 42% uptake could amount to €2.68 million (95% CI: €1.27 million to €3.91 million), through 1,178 (95% CI: 550 to 1,783) RSV-related hospital bed days averted, of which 276 (95% CI: 117 to 463) relate to a hospital discharge which included an ICU stay.

Table 5.16 Mean costs associated with maternal immunisation with RSVpreF at varying unit costs and uptake rates

Uptake %	Mean costs of maternal immunisation with RSVpreF at various uptake rates and costs (95%CI) (€ in millions)*						
	RSVpreF cost (€165 plus 23% VAT)	RSVpreF cost (€160 plus 23% VAT)	RSVpreF cost (€155 plus 23% VAT)	RSVpreF cost (€150 plus 23% VAT)	RSVpreF cost (€145 plus 23% VAT)	Administration fee (€25)	NCCS costs~
Maternal immunisation strategy							
42%	2.35 (1.52 to 3.36)	2.29 (1.47 to 3.25)	2.24 (1.45 to 3.20)	2.15 (1.40 to 3.11)	2.08 (1.35 to 2.98)	0.29 (0.19 to 0.42)	0.02
47%	2.63 (1.70 to 3.75)	2.56 (1.65 to 3.64)	2.51 (1.63 to 3.58)	2.41 (1.56 to 3.48)	2.33 (1.51 to 3.34)	0.33 (0.21 to 0.47)	0.02
52%	2.91 (1.88 to 4.15)	2.84 (1.82 to 4.03)	2.78 (1.80 to 3.96)	2.67 (1.73 to 3.85)	2.58 (1.67 to 3.69)	0.36 (0.23 to 0.52)	0.02
57%	3.19 (2.07 to 4.55)	3.11 (2.00 to 4.42)	3.05 (1.97 to 4.34)	2.92 (1.89 to 4.22)	2.82 (1.83 to 4.05)	0.40 (0.26 to 0.57)	0.03
62%	**3.47 (2.25 to 4.95)**	3.38 (2.17 to 4.80)	3.31 (2.15 to 4.72)	3.18 (2.06 to 4.59)	3.07 (1.99 to 4.40)	**0.43 (0.28 to 0.62)**	**0.03**

Key: CI – confidence interval; NCCS – National Cold Chain Service; VAT – value-added tax.
*Mean costs exclude fixed costs associated with programme implementation.
~NCCS costs relate specifically to volume of products processed by NCCS as part of these strategies.

Table 5.17 Summary of health outcomes that could be avoided at varying maternal immunisation uptake rates

Projected RSV immunisation uptake rate (%)	Mean number of notified RSV cases avoided (n)	Mean number of RSV-related hospital discharges avoided (n)	Mean number of RSV-related hospital discharges which include an intensive care unit stay avoided (n)	Mean number of RSV-related deaths avoided (n)	Mean RSV-related hospital bed days avoided (n)	Mean RSV-related hospital bed days which included an intensive care unit stay avoided (n)	Mean RSV-related hospital costs avoided (€ million)
42%	361 (228 to 470)	275 (131 to 391)	25 (12 to 39)	0 (0 to 0)	1,178 (550 to 1,783)	276 (117 to 463)	2.68 (1.27 to 3.91)
47%	404 (255 to 526)	307 (147 to 437)	29 (13 to 43)	0 (0 to 0)	1,319 (615 to 1,995)	309 (131 to 519)	2.99 (1.42 to 4.38)
52%	447 (282 to 582)	340 (163 to 484)	32 (15 to 48)	0 (0 to 0)	1,459 (681 to 2,207)	342 (145 to 574)	3.31 (1.57 to 4.84)
57%	490 (309 to 638)	373 (178 to 531)	35 (16 to 52)	0 (0 to 0)	1,599 (746 to 2,419)	375 (159 to 629)	3.63 (1.72 to 5.31)
62%	**532 (336 to 694)**	**406 (194 to 577)**	**38 (17 to 57)**	**0 (0 to 0)**	**1,739 (812 to 2,631)**	**408 (173 to 684)**	**3.95 (1.88 to 5.77)**

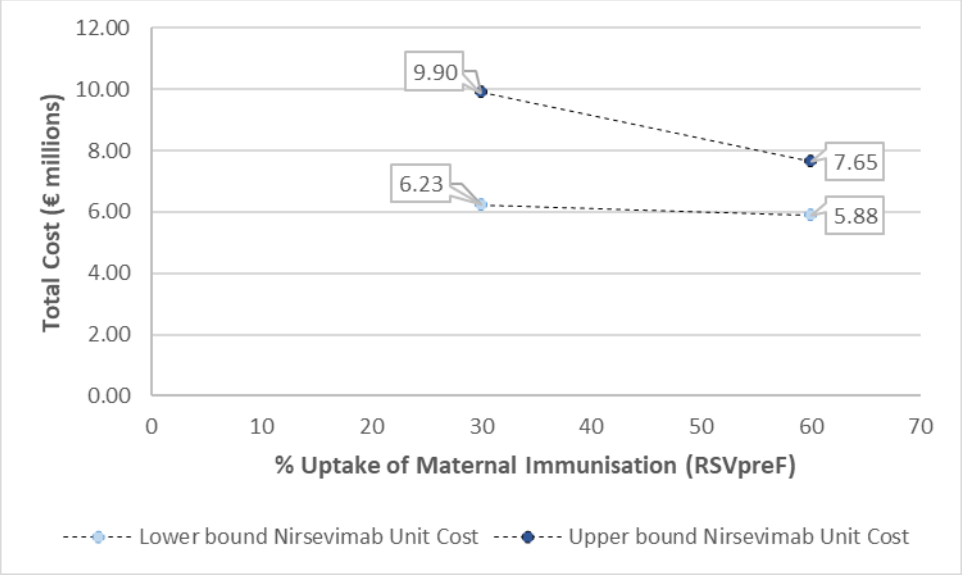
Key: n – number; RSV – respiratory syncytial virus.

As previously outlined, costing a range of combination strategies was considered beyond the scope of this analysis. Figure 5.4 below provides an indication of costs that might be associated with a combined strategy, which aims to provide passive immunisation to infants born during the RSV season (from September to February). The estimates shown indicate the total cost of offering both the maternal vaccine to pregnant women expected to give birth during the RSV season (for both 30% and 60% uptake), and offering nirsevimab to the remaining eligible infant cohort, to achieve an overall coverage rate of 88% in those infants born during the RSV season. The ex-VAT unit cost of the maternal vaccine was assumed to be as per the base-case analysis (€165), while that of nirsevimab was taken at the lower and upper bounds of the range used in the scenario analysis (€209 and €393, respectively).

If a combination strategy was offered, and assuming 30% maternal immunisation uptake, the total cost of achieving 88% immunisation coverage in infants born during the RSV season was estimated to be €6.23 million (if nirsevimab was procured at a unit cost of €209), and €9.9 million (if nirsevimab was procured at a unit cost of €393). In contrast, if a maternal immunisation uptake of 60% is assumed, the total cost of achieving 88% immunisation coverage for the combination strategy was estimated to be €5.88 million (if nirsevimab was procured at a unit cost of €209), and €7.65 million (if nirsevimab was procured at a unit cost of €393.24).

Notably, these estimates are based on costs per unit delivered only, and do not consider any wastage related to unused stock. While this is a consideration for all estimates provided in this analysis, it is particularly notable when considering a scenario where there is bulk procurement of the maternal vaccine, given the substantial uncertainty in relation to uptake of this strategy.

Figure 5.4 Scenario analysis of estimated expenditure associated with offering a combined maternal and infant immunisation strategy at varying maternal vaccine uptake rates



Potential costs associated with active immunisation of adults aged 65 years

As part of a scenario analysis, Table 5.18 presents the potential costs related to procurement and administration fees payable (at varying uptake rates and varying unit costs) to the HSE associated with introducing an RSV immunisation programme, using either RSVpreF or RSVPreF3, targeting adults aged 65 years and older. These estimates use a projected eligible population of 840,830, with the ex-VAT unit cost of the vaccine varied from €145 to €165 and uptake varied from 66% to 86%.

Compared with the base case (which assumed vaccine uptake of 76% and ex-VAT unit cost of €165) where the cost of vaccine procurement was estimated at €129.0 million (95% CI: €83.5 million to €184.6 million), the cost of vaccine procurement was estimated at €114.1 million (€74.3 million to €162.7 million) if the ex-VAT unit cost is €145 assuming the same uptake. The administration fees, at this same uptake rate (76%), were estimated to be €16 million (95% CI: €10.3 million to €22.8 million).

Potential costs associated with active immunisation of adults aged 75 years

As a scenario analysis, Table 5.19 presents the potential costs related to procurement and administration fees (at varying uptake rates and unit costs) to the HSE if implementation is limited to adults aged 75 years and older using either RSVpreF or RSVPreF3. These estimates use a projected population of 381,856, with

the ex-VAT unit cost of the vaccine varied from €145 to €165 and uptake varied from 77% to 97%.

Compared with the base case (which assumed vaccine uptake of 87% and an ex-VAT unit cost of €165) where the cost of vaccine procurement was estimated at €67.3 million (95% CI: 43.1 million to €96.7 million), the cost of vaccine procurement was estimated at €59.3 million (€38.3 million to €84.4 million) if the ex-VAT unit cost is €145 assuming the same uptake. The administration fees, at this same uptake rate (87%), were estimated to be €8.3 million (95% CI: €5.4 million to €11.9 million).

Table 5.18 Mean one-year costs associated with the immunisation of adults aged 65 years and older at varying unit costs and uptake rates

Uptake %	Mean costs of immunisation of adults aged 65 years and older at various uptake rates and costs (95%CI) (€ in millions)						
	Vaccine cost (€165 plus 23% VAT)	Vaccine cost (€160 plus 23% VAT)	Vaccine cost (€155 plus 23% VAT)	Vaccine cost (€150 plus 23% VAT)	Vaccine cost (€145 plus 23% VAT)	Administration fee (€25)	NCCS costs*
Adults aged 65 years and older – RSVpreF and RSVPreF3							
66%	112.0 (72.5 to 160.3)	108.9 (70.4 to 154.7)	106.0 (68.8 to 152.3)	102.4 (65.8 to 145.8)	99.1 (64.5 to 141.3)	13.9 (8.9 to 19.8)	1.0
71%	120.5 (78.0 to 172.4)	117.2 (75.7 to 166.4)	114.1 (74.0 to 163.8)	110.2 (70.8 to 156.8)	106.6 (69.4 to 152.0)	14.9 (9.6 to 21.3)	1.0
76%	**129.0 (83.5 to 184.6)**	125.4 (81.1 to 178.1)	122.1 (79.2 to 175.4)	117.9 (75.7 to 167.8)	114.1 (74.3 to 162.7)	**16.0 (10.3 to 22.8)**	**1.1**
81%	137.5 (89.0 to 196.7)	133.7 (86.4 to 189.9)	130.1 (84.5 to 186.9)	125.7 (80.7 to 178.9)	121.6 (79.2 to 173.4)	17.0 (11.0 to 24.3)	1.2
86%	145.9 (94.5 to 208.9)	142.0 (91.7 to 201.6)	138.1 (89.7 to 198.5)	133.5 (85.7 to 189.9)	129.1 (84.0 to 184.1)	18.1 (11.7 to 25.8)	1.2

Key: CI – confidence intervals; NA – not applicable; VAT – value-added tax.
*NCCS costs relate specifically to volume of products processed by NCCS as part of these strategies.

Table 5.19 Mean one-year costs associated with the immunisation of adults aged 75 years and older at varying unit costs and uptake rates

Uptake %	Mean costs of immunisation of adults aged 75 years and older at various uptake rates and costs (95% CI) (€ in millions)						
	Vaccine cost (€165 plus 23% VAT)	Vaccine cost (€160 plus 23% VAT)	Vaccine cost (€155 plus 23% VAT)	Vaccine cost (€150 plus 23% VAT)	Vaccine cost (€145 plus 23% VAT)	Administration fee (€25)	NCCS costs*
Adults aged 75 years and older – RSVpreF and RSVPreF3							
77%	59.5 (38.2 to 85.6)	58.0 (37.6 to 82.3)	55.9 (36.2 to 79.4)	54.4 (35.4 to 78.2)	52.5 (33.9 to 74.7)	7.4 (4.8 to 10.5)	0.5
82%	63.4 (40.7 to 91.1)	61.7 (40.1 to 87.7)	59.6 (38.5 to 84.5)	57.9 (37.7 to 83.3)	55.9 (36.1 to 79.6)	7.8 (5.1 to 11.2)	0.5
87%	**67.3 (43.1 to 96.7)**	65.5 (42.5 to 93.0)	63.2 (40.9 to 89.7)	61.4 (40.0 to 88.4)	59.3 (38.3 to 84.4)	**8.3 (5.4 to 11.9)**	**0.6**
92%	71.1 (45.6 to 102.3)	69.3 (45.0 to 98.4)	66.8 (43.2 to 94.9)	65.0 (42.3 to 93.5)	62.7 (40.5 to 89.3)	8.8 (5.7 to 12.6)	0.6
97%	75.0 (48.1 to 107.8)	73.1 (47.4 to 103.7)	70.5 (45.6 to 100.0)	68.5 (44.6 to 98.5)	66.1 (42.7 to 94.1)	9.3 (6.0 to 13.3)	0.6

Key: CI – confidence interval; NCCS – National Cold Chain Service; VAT – value-added tax.
*NCCS costs relate specifically to volume of products processed by NCCS as part of these strategies.

5.3.3 One-way sensitivity analysis (OWSA)

Results of the OWSA conducted on the base-case results for total costs of each strategy are presented as tornado plots in Appendix 5A. As described in 5.2.11, this deterministic OWSA aims to identify parameters to which the basecase result in each strategy is most sensitive. Six input parameters (that is, immunoprophylaxis uptake rate, clinical effectiveness, incidence of disease, likelihood of hospital discharge (any), cost of hospital discharge, and assumed product unit cost) were varied individually by fixing them in turn at their upper and lower bounds, while all other parameters were held at their mean. In each of the strategies assessed, relating to either the passive immunisation of the general infant population, or active immunisation of older adults, the estimates of total costs were most sensitive to cost of product procurement (that is, to the assumed unit cost per product). It is noted however that the maternal immunisation strategy also showed comparable sensitivity to the estimate of vaccine effectiveness.

5.4 Discussion

5.4.1 Results of the costing analysis

Immunisation of children at increased risk of severe LRTD associated with RSV

Based on the assumptions used in this analysis, at all costs of nirsevimab assessed (ranging from a unit cost of €209.00 to €393.24 ex-VAT), switching to a strategy that offers passive immunisation with nirsevimab to children currently eligible to

receive palivizumab would likely cost less than the current standard of care. While a range of unit costs for nirsevimab were considered, it is noted that there is substantial uncertainty in relation to its cost as it is not currently marketed in Ireland. Cost estimates were therefore based on reported international costs, acknowledging that these varied markedly. There is greater certainty in relation to the procurement cost of palivizumab with the mean annual drug costs (ex-VAT) estimated at approximately €3,200 per infant aged less than one, and €2,900 per child aged less than two years.

Available data indicate that the population availing of palivizumab is relatively small (240 individuals aged less than one year and 580 individuals if considering those aged less than two years). The analysis was robust to 5% and 10% increases in these estimated patient populations. The analysis assumed comparable effectiveness and safety for nirsevimab and palivizumab, and as such it did not include potential for differences in costs offsets (for example, more or fewer hospital discharges). However, it is not known if a switch to nirsevimab (single dose at the start of the RSV season) from palivizumab (monthly doses during the RSV season) would lead to more complete protection for some children, given the potential for non-adherence with recommended palivizumab dosing schedules. It was assumed that there would be no programme costs for the NIO if a decision in relation to RSV immunisation is limited to a change in health technology for this population at increased risk.

Immunisation programmes involving the passive immunisation of the general infant population against RSV

For immunisation strategies targeting the general infant population, given the assumptions in this analysis, it was estimated that the incremental cost to the HSE would range from €2.54 million (95% CI: - €1.17 to €6.80 million) to €5.45 million (-€1.96 to €13.97 million) for strategies involving nirsevimab administration to a saving of €0.01 million (95% CI: -€2.24 million to €2.43 million) for a strategy based on maternal immunisation. There is substantial uncertainty associated with these estimates as indicated by the wide confidence intervals, with most of this driven by uncertainty in relation to the cost of nirsevimab. To reflect this uncertainty, a range of costs informed by the international literature were modelled to show how the cost of the alternative strategies may vary. Scenario analysis indicated that at the maximum unit cost accounted for in the model (€393.24 ex-VAT), the cost of procuring nirsevimab would increase by between €2.8 and €5.4 million depending on the strategy. Further increases in the unit cost above the maximum modelled cost would lead to proportional increases in the cost of any nirsevimab-based programme.

The estimated impact of effective alternate immunisation strategies on healthcare utilisation and hospital costs associated with RSV in infants aged less than one year is notable and expected given the high burden of disease experienced by infants aged less than one year (as previously outlined in Chapter 4). A seasonal infant strategy was estimated to lead to 696 (range: 536 to 863) hospital discharges avoided and 2,992 (2,134 to 4,006) hospital bed days avoided. Considering specifically discharges that include an ICU stay, it was estimated to avert, on average, 65 (range: 45 to 87) hospital discharges and a total of 700 (range: 422 to 1,071) bed days which include an ICU stay. The corresponding impact for a seasonal plus catch-up strategy (that is, offering immunisation to all infants in their first RSV season) was that it would, on average, avert 1,393 (range: 1,078 to 1,718) hospital discharges and 5,973 (range: 4,255 to 7,391) hospital bed days in those with a primary diagnosis of RSV. For discharges that include an ICU stay, the seasonal plus catch-up strategy was estimated to avert, on average, 129 (range: 91 to 174) discharges and 1,404 (range: 844 to 2,132) total bed days. These potential impacts on the organisation and effective delivery of paediatric secondary care are all the more notable considering the distribution of RSV hospitalisations. As outlined in Chapter 4, considering a population aged 0 to 4 years, HIPE data for the period 2013 to 2022 indicate that, on average, infants aged less than one year accounted for 84% of discharges that did not include an ICU stay and 90% of discharges that included an ICU stay. Moreover, the majority of discharges in those aged 0 to 4 years occur in quarter four (October to December) each year, ranging from 71% in 2018 to 91% in 2021 (of those without an ICU stay), and from 61% in 2018 to 91% in 2021 (of those that included an ICU stay). When a high number of cases require hospital care, and in particular ICU care, this has the potential to overwhelm available capacity, reducing the ability to provide scheduled care. Based on healthcare patterns over the last 10 years, it is likely that the greatest impact of an RSV immunisation programme on secondary healthcare services would be seen in quarter four each year. Accordingly, a hybrid approach to immunisation was also modelled in this costing study which considered the immunisation of infants born during the period from June to December each year. This could provide an alternative to seasonal immunisation and to immunisation of all infants (seasonal plus catch-up) if the latter were considered not feasible due to cost or programmatic reasons.

It was estimated that while maternal immunisation would also avert considerable RSV-related health outcomes and hospital discharge costs, the impact would be lower compared with nirsevimab-based strategies for those born within the RSV season. This is due to the lower uptake rate assumed for maternal immunisation (62% vs. 88% for immunisation with nirsevimab), and the lower reported efficacy of

the maternal vaccine compared with nirsevimab (70.9% (95% CI: 44.5% to 85.9%) vs. 80% (95% CI: 70% to 87%)). At the assumed base-case price for the maternal vaccine, when uptake rates for the maternal immunisation strategy were varied (42% to 88%), it was noted that the cost to procure and administer the maternal vaccine would remain broadly comparable to the hospitalisation cost offsets that would be achieved.

It is acknowledged that an alternative approach to that modelled could also be considered. This would offer nirsevimab to those infants not protected by maternal immunisation (that is, to infants born to mothers who did not avail of the maternal vaccine or whose immunisation status is unknown or for infants born less than 14 days following immunisation). This combined approach, recommended by the US CDC, would result in a higher number of infants protected through passive immunisation, and accordingly both higher procurement costs and higher cost offsets due to a higher number of RSV-related outcomes averted.

Immunisation programmes involving the immunisation of adults aged 65 years and older, and 75 years and older, against RSV

For immunisation strategies targeting the older adult population, given the assumptions in this analysis, it was estimated that the one-year incremental cost to the HSE would range from €75.2 million (95% CI: €51.0 million to €104.6 million) for a strategy based on providing RSVpreF to those aged 75 years and older to €144.9 million (95% CI: €99.1 million to €200.5 million) for a strategy based on RSVPreF3 to all adults aged 65 years and older. The large incremental cost relates to the size of the eligible population (n=840,830 ≥65 years; n=381,856 ≥75 years), the assumed cost of the vaccine (€165 ex-VAT), the assumed cost of administering the vaccine in primary care (€25) and the limited potential to avert hospital healthcare utilisation given the low annual number of hospital discharges relating to a primary diagnosis of RSV in this age group (n=225 in adults aged 65 years and older vs. n=12,065 in infants aged 0 to 4 years from 2013 to 2022). Differences in the incremental costs associated with the two different vaccines relate to differences in the assumed vaccine efficacy (88.9% (95% CI: 53.6% to 98.7%) for RSVpreF vs. 82.6% (96.95% CI: 57.9% to 94.1%) for RSVPreF3). Again, there is substantial uncertainty associated with these estimates as indicated by the wide confidence intervals.

As outlined in Chapter 4, the number of hospitalisations in older adults with a primary diagnosis of RSV is small relative to the burden in infants aged less than one year. Therefore the potential for cost offsets related to hospital discharges averted are limited. However, the population aged 65 years and older are not homogenous, with Chapter 4 noting that burden associated with RSV increases with age.

Accordingly, the costing analysis indicated that if immunisation is limited to the cohort of individuals aged 75 years and older, approximately 60% fewer individuals would be vaccinated, but this approach would still accrue, on average, approximately 80% of the benefits in terms of hospital discharges averted and would avert approximately 92% of the bed days.

It is noted that data relating to hospital discharge costs were supplied for adults aged 65 years and older only, and were not further disaggregated by age. Thus the same discharge cost was applied in the analysis for both adults aged 65 years and older and those aged 75 years older. However, HIPE data indicate that the average length of stay is slightly longer in adults aged 75 years and older, suggesting that the costs averted from reduced RSV-related hospital discharges may be underestimated in this group and conversely that they may be overestimated when considering the total population aged 65 years and older. While acknowledging this, it does not have a significant impact on the overall one-year cost given their small contribution relative to vaccine procurement and administration fees.

In Ireland, both RSV vaccines considered in this assessment are authorised for use in older adults and available to purchase on foot of a private prescription. If an immunisation programme targeting older adults was to be considered, the choice of vaccine may be dependent on the results of a competitive tender process.

5.4.2 Limitations of the costing analysis

RSV is a contagious disease, which is transmissible through respiratory droplets and direct contact with an infected individual. This costing analysis is limited to determining the impact of different immunisation strategies on RSV burden in the target populations and HSE. This analysis does not account for changes in virus transmission, existing contact patterns and herd protective effects that may be observed as a result of adopting any of the RSV immunisation strategies assessed. Such effects may be estimated through analysis with an epidemiological model.

As noted in Chapter 4, with the exception of the number of notified RSV cases, the outcome data considered are limited to hospital-based care and therefore underestimate the burden of RSV in the community. The analysis does not include costs averted due to reduction in GP attendance associated with RSV. Moreover, the data relating to RSV-related hospital discharges used in this costing analysis are limited to those with a primary diagnosis of RSV. These data focus on hospital discharge data and therefore exclude potential costs averted associated with ED attendance that do not result in an admission. The HIPE data pertaining to hospital discharges indicate the number of discharges with and without an ICU stay, reported separately, and the average length of stay for these discharges. However, these

data lack information specific to the number of bed days a patient spends in ICU out of their total hospital stay. Changes to the duration of time spent in ICU would impact the mean cost of discharge, and as such, another limitation of the analysis is that any reduction in severity of the disease experienced by an individual may not be accurately captured. Furthermore, secondary diagnoses were excluded from the analysis, as it could not be said with certainty that RSV was a contributor to hospitalisation. As outlined in Chapter 4, there have been substantial changes in testing practices in recent years with increased capacity for (and presumably use of) multiplex RT-PCR testing for those presenting with respiratory tract infections. This may result in improved detection of RSV, with a higher proportion of the current secondary care burden (for example, admissions due to acute bronchiolitis in children or due to lower RTI in adults) being attributed to RSV. Therefore, the results of the costing analysis likely provide a conservative estimate of the health outcomes averted as a consequence of any immunisation programme.

Assumptions were made in this analysis as to the administration fees payable to primary care contractors (that is, GPs and community pharmacies) per dose administered, which were estimated based on existing HSE contractor payment agreements for vaccine administration. Any agreements regarding fees payable may be subject to negotiation with professional representative groups as part of a primary care agreement and could differ from the values assumed in this analysis given the seasonal burden and the fact that nirsevimab is not a vaccine. Additionally, it is noted that, for simplicity, this analysis did not separately cost the delivery of RSV vaccines by HSE Vaccination Teams to eligible adults resident in LTCFs. Instead, the same administration cost (€25) was applied in the base case to all RSV vaccinations for eligible older adults, with this amount based on existing contractor administration fee agreements for adult seasonal vaccines. While recognising that costs in the LTCF setting may differ and that an administration fee would not be paid as vaccination would be undertaken by HSE staff, it is noted that the cost of administration was not a driver in these models and moreover that this cohort likely represent a minority of all potential eligible older individuals given approximately 32,000 registered nursing home beds in Ireland.[355]

While parameter values can be varied in a range as part of sensitivity analyses, a costing analysis cannot account for any changes in parameters over the time horizon of one year. The effectiveness estimate used in this model is assumed to be constant, though varied within a range. In reality, effectiveness may wane with time after product administration (in the case of nirsevimab or active immunisation of older adults), or after birth (in the case of passive immunisation through maternal vaccination). EPAR reports for nirsevimab and for the maternal vaccine indicate waning immunity over 150-[9] or 180-[8]day periods, respectively. For the infant

strategies (in the general population) assessed in this analysis, parameters relating to clinical effectiveness of nirsevimab and the maternal vaccine relate to effectiveness at 150 days, and so it would be expected that model estimates of cases averted and hospitalisations averted are, in fact, conservative estimates.

The effectiveness estimate for nirsevimab used in this analysis specifically relates to effectiveness observed in infants entering their first RSV season. The efficacy of nirsevimab has not yet been proven in children entering their second RSV season, though, as outlined in Chapter 2, in June 2024, the EMA's CHMP has given their positive opinion on a Type II variation request regarding extension of the authorised indication to include treatment of children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[48] Additionally, with respect to the immunisation of infants at increased risk of severe RSV disease, in the absence of head-to-head trial data, it was assumed that palivizumab and nirsevimab were equally effective in this cohort. However, this may not be the case.

In the case of infant populations, data were only available in one-year age bands. It was not possible to distinguish between infants aged less than six months and those aged six to 12 months. It was also not possible to analyse specific subgroups, such as those at increased risk of disease who are currently eligible to receive palivizumab, as risk status is not routinely collected within the data. As such, data used in this analysis provided no indication of any risk status or co-morbidities of these infants. In the analysis, infants at increased risk of RSV disease were conservatively assumed to have the same risk of infection and hospitalisation as that observed in the general infant population. Additionally, all infants aged under one year were assumed to have the same risk of infection and hospitalisation, regardless of month of birth, or age during the RSV season. While these are notable limitations of the available data used, the modelled results may underestimate the true burden of disease in the modelled high-risk and under-six-months-of-age populations.

In the case of adult immunisation, vaccine efficacy has been reported by both manufacturers into the second season.[356, 357] Consideration of product effectiveness into a second year is beyond the scope of this one-year costing analysis, however it is noted that the impact of vaccination of older adults may be experienced over a second season (that is, sustained protection against RSV). While sustained protection could mean that annual RSV immunisation is not required, as yet, these data are uncertain.

In this analysis, one figure representing overall immunisation uptake in the specified eligible populations was applied, whereas in reality, immunisation uptake may vary throughout a season. Decreased burden of hospitalisation in Galicia, Spain following the introduction of nirsevimab for the 2023-2024 RSV season has been attributed to

the success of early monoclonal antibody uptake — that is, completing immunisation for the majority of infants in the catch-up cohort prior to the start of the RSV season.[312] Additionally, those born during the RSV season were offered nirsevimab at the earliest opportunity (typically on day two, prior to hospital discharge) which was considered important, given that it takes approximately two weeks for the infant to develop a sufficient level of immunity following immunisation.[8] Similarly, in the case of the maternal vaccine, maximum levels of immunity develop in the in-utero infant two weeks after maternal immunisation.[9, 126] If the infant is born within two weeks of maternal immunisation, and so prior to achieving this maximum level of immunity, they may still require administration of palivizumab or nirsevimab at birth. As noted, this costing analysis does not consider the potential for such a circumstance.

It should be considered that uptake of the maternal vaccine in particular may be lower than estimated for a number of reasons. Firstly, immunisation against RSV is a comparatively new concept both in Ireland and worldwide, owing to the fact that technologies which provide immunoprophylaxis against RSV in the general population have only received market authorisation at varying time-points in the past two years. There may be a lack of understanding as to why immunisation against RSV may be beneficial, or reluctance on the part of an expectant mother to be vaccinated. Secondly, because the maternal vaccine is a new technology in itself (marketing authorisation in EU/EEA received September 2023), there may be further hesitancy on the part of the expectant mother, owing to concerns she may have around safety or around the limited post-authorisation surveillance data, compared with, for example, pertussis or influenza vaccination, which have been offered to expectant mothers for many years, and for which safety is well-established.

Estimates of efficacy used in this analysis were sourced from published RCTs. HPSC data relating to notified cases of RSV were used as a proxy for the number of medically attended visits in Ireland. HIPE data were used to estimate the proportion of notified cases that are hospitalised or require admission to ICU. Therefore, in the analysis, the efficacy of these strategies relates to their impact on reducing the incidence of notified cases. It was assumed that reductions in hospitalisation and admission to ICU are directly proportional to reductions in incidence.

Importantly, while some efficacy estimates used for strategies in this analysis relate to reduction in RSV-associated hospitalisations, others relate to reduction in severe disease caused by RSV. In the case of nirsevimab-based strategies, while case definitions for RSV-associated hospitalisations were not identical between the RCTs, they were considered sufficiently comparable, to allow a pooled estimate for nirsevimab to be calculated. In the case of the maternal vaccine, the case definition

of medically-attended severe RSV-associated LRTI[126] most closely reflected the definition for RSV-associated hospitalisations as described in the nirsevimab trials, and was considered to provide the most comparable measure of efficacy. While the MATISSE trial interim results reported an estimate relating to the efficacy of RSVpreF at reducing hospitalisation due to RSV, there was one more case of hospitalisation reported in the RSVpreF intervention group (17/3,495) than that of those reported as a having medically-attended severe RSV-associated LRTI (16/3,495). As such, it could not be said that the maternal vaccine has a different effectiveness against hospitalisation than it does for medically-attended severe RSV-associated LRTI. Therefore, in this analysis, it was assumed that, while maternal immunisation reduces incidence of RSV, it does not further reduce the likelihood of hospitalisation in the infant cohort benefiting from passive immunisation. As reductions in hospitalisation and admission to ICU in this analysis are considered directly proportional to reductions in incidence, the resulting hospital costs averted may be either overestimated, or underestimated, in the case of a maternal strategy. While this is a limitation of the analysis, it is plausible that reduced incidence of severe RSV would result in fewer hospitalised cases. Of note, the estimates above are based on the interim results of the MATISSE trial; the MATISSE trial has since concluded (in October 2023),[125] and publication of final results from the trial may report further vaccine efficacy against hospitalisation for RSV, which could in turn impact the total one-year cost estimates reported in this analysis. While nirsevimab and the maternal vaccine have demonstrated efficacy against RSV-associated hospitalisations, the RCTs for vaccination of older adults do not include reduced RSV-associated hospitalisations as an efficacy outcome. Instead, efficacy estimates used in immunisation strategies targeting older adults in this analysis relate to efficacy of the RSV vaccines at reducing medically-attended visits due to RSV-associated LRTD. While it cannot be said with certainty that vaccination of older adults will result in reduced hospitalisations, this analysis assumed that reduction in RSV-associated hospitalisation was in fact directly proportional to reduction in incidence. Again, this is a limitation of the analysis, but it was considered plausible that where the vaccine successfully reduces incidence of severe RSV cases, it would likely also proportionally reduce RSV-associated hospitalisations. It should be noted that the primary objective of this analysis is to provide an estimation of the costs associated with delivering immunisation against RSV, though it is helpful to consider how the overall costs may be affected when potential hospital costs averted are considered.

In this analysis, costs associated with adverse events that may occur after administration of any of the health technologies considered were not included in the analysis, as the risk of serious adverse events was deemed minimal, based on the available (industry-funded) RCT data, as outlined in Chapter 3. As the new immunoprophylaxis agents have only recently received marketing authorisation,

there is little real-world evidence available to provide further evidence on the occurrence of adverse events associated with these technologies, though recent evidence relating to nirsevimab in Galicia supports the favourable safety profile assumed in this analysis.[312] Should evidence of harms that require healthcare utilisation (for example, ED visits and hospitalisation) emerge as a result of using these technologies, this would have implications for the cost of these programmes.

There are a number of additional limitations of the analysis relating to available data. For infants currently receiving palivizumab, PCRS data provide information on doses reimbursed through primary care settings only. The available PCRS data suggest that, on average, infants aged less than one year receive 3.3 vials of palivizumab per annum, and infants under less than two years of age receive 3.4 vials of palivizumab per annum. However, some infants may receive one or more doses of palivizumab as an inpatient in a secondary care setting. These data are unknown as there is no centralised database of palivizumab usage in secondary care. This costing analysis assumed that children aged less than one year received one dose in hospital, and as such, receive an average of 4.3 vials per annum. While noting that palivizumab should be administered monthly during an RSV season (up to five doses), this analysis may overestimate the cost of supplying palivizumab to an eligible infant and therefore overestimate the savings that would accrue from a switch to nirsevimab. Additionally, it is possible that a patient may receive all doses of palivizumab through an inpatient setting, and if so, the number of unique patients estimated as part of this analysis would not capture these patients. However, scenario analyses conducted at a 5% to 10% increase in the eligible infant populations should mitigate some uncertainty regarding this.

At present, children considered at increased risk of LRTD associated with RSV are prescribed palivizumab by a consultant physician, who may make a decision to prescribe based on NIAC Guidelines, internal hospital formulae, or both.[76] There is a risk that, should a national RSV immunisation programme targeting this cohort be implemented, prescribing patterns may alter, and the resulting population deemed eligible to receive nirsevimab would be higher than that estimated in this analysis. Consequently, product costs would also be higher than those estimated.

5.4.3 Organisational considerations

While this costing analysis made assumptions regarding the implementation of each of the immunisation strategies assessed, it is important to note that any decisions relating to the funding and delivery of any immunisation programme (including any organisational decisions relating to implementation) are the responsibility of the Department of Health and the Health Service Executive.

It was assumed in this costing analysis that strategies involving infant immunisation with nirsevimab may involve delivery in either primary or secondary care settings. For strategies delivered in a maternity unit and or hospital, it would be important to consider existing staffing capacity and constraints at these sites. The number of births anticipated in these hospitals will impact staffing demands relating to product administration and post-administration monitoring. Based on feedback from the 2023-2024 nirsevimab pilot in Galicia, the costing analysis considered that immunisation against RSV would take an additional 15 minutes of a healthcare professional's time. Considering the distribution of total births for 2021, the labour costs required per week for the 2025-2026 RSV season were estimated to range from an average of 4 to 44 hours per week across the 19 maternity hospitals and or units during the RSV season.

Offering immunisation against RSV in the first few days of life alongside other routine clinical assessments, such as the newborn heel prick test, could provide an opportunity to immunise infants early in life and may facilitate optimal uptake rates. Only 178 parents and or guardians are known to have declined the offer of the newborn bloodspot screening program between the years 2020-2022 inclusive,[306] indicating that 99.9% of parents participate, and so attend the appointment for sample collection. Similarly, offering immunisation with nirsevimab alongside routine primary childhood immunisation to those infants entering their first RSV season may also encourage comparable uptake rates (88.1% at 12 months across all scheduled vaccines).

For costing purposes, it was assumed that immunisation with nirsevimab offered to infants born outside of an RSV season — that is, the 'catch-up' cohort — would be delivered through primary care settings, during the weeks immediately preceding the start of the anticipated RSV season, with the aim to maximise uptake prior to the start of the RSV season.

Another approach for this cohort, though not costed in this analysis, would be to offer immunisation with nirsevimab through dedicated hospital-based catch-up clinics (within maternity units and or hospitals) that would operate for a defined time frame. This approach was undertaken in Galicia (Spain), where nirsevimab was offered to all infants aged less than six months at the start of the 2023-2024 RSV season.[86] Electronic appointments were issued to invite this cohort for immunisation at their hospital of birth, with appointments scheduled within three weeks of commencement of the immunisation campaign. After this three-week period, any remaining eligible infants who did not present for an appointment could then avail of nirsevimab immunisation in a primary care setting by a registered GP.[86] This catch-up cohort comprised 7,354 eligible infants in total, and

immunisation coverage of 77.1% (n=5,670) was achieved after three weeks.[92] While this catch-up clinic-based strategy achieved high uptake rates in a condensed period, it is noted that the estimated eligible catch-up cohort in Ireland is substantially larger (approx. 28,000 infants). Furthermore, as outlined in section 5.2.10, the distribution of births across Ireland varies markedly between maternity units and or hospitals, with four maternity hospitals accounting for over half of all deliveries annually. As such, there would likely be significant organisational challenges associated with providing hospital-based catch-up clinics both in terms of recruiting staff for short-term contract work to resource the clinics and potential for capacity issues in some hospitals in relation to the physical space to house the temporary clinics. The latter could result in additional overhead costs if temporary clinics have to be set up off-site. While not costed in this rapid HTA, hospital-based catch-up clinics remain another option for programme implementation.

It was proposed that maternal immunisation against RSV be delivered in a primary care setting. All pregnant women who are ordinarily resident in Ireland are entitled to free medical care relating to their pregnancy under the Mother and Infant Care Scheme.[358] As part of this scheme, pregnant women fall under the care of both a GP and obstetrician, and may be expected to attend approximately six examinations with their GP prior to birth.[358] However, where other risk factors or comorbidities are present, pregnant women may attend their maternity unit or hospital more regularly than usual to receive specialist care relating to the management of their pregnancy and or any accompanying medical conditions. Expert opinion provided by EAG members has indicated that, in such circumstances, pregnant women may attend primary care appointments less frequently, this may increase the risk of immunisation not being offered or availed of within the appropriate immunisation window. Any immunisation programme targeting pregnant women should consider how best to ensure optimal uptake rates in the maternal population. The foetal anatomy scan, which is typically scheduled at 20 gestational weeks, may provide an opportunity for either an obstetrician or midwife to initially discuss maternal immunisation against RSV with an expectant mother. This appointment may also provide an opportunity to highlight to an expectant mother the precise timeframe whereby immunisation should be availed of, encourage her to engage with primary care services for additional information and, if interested, make an appointment with her GP for immunisation. A further option for delivery of a maternal immunisation strategy, though not costed as part of this analysis, would be to offer maternal immunisation through maternity units and or hospitals only. Delivery of maternal immunisation in this way could be advantageous as it would offer an opportunity to facilitate centralised record-keeping of maternal vaccine uptake. However, it would require all pregnant women to return to the maternity unit and or hospital within the appropriate immunisation window, and a matter of weeks after their foetal anatomy

scan. This may pose an additional logistical challenge to the expectant mother, particularly as, for the majority of uncomplicated cases, they will already be scheduled to attend their GP for a routine medical examination within the specified immunisation window.

The acceptability of introducing a novel immunisation programme against RSV may differ between the various target patient groups, and could also pose a barrier to successful programme implementation. As outlined previously, adults aged 65 years and older are already eligible for two other seasonal immunisation programmes (influenza and COVID-19). In this analysis, an uptake rate of 76% was assumed in the base-case analysis for adults aged 65 years and older, and 87% for adults aged 75 years and older. There is a risk that increased immunisation demands on this adult cohort may result in vaccine fatigue,[359] and consequently lower the anticipated uptake of any of the seasonal immunisation programmes offered. As previously discussed, there are no reliable estimates to inform maternal vaccine uptake in Ireland and, as outlined in Chapter 4, international uptake rates in this population vary both by country, and vaccine offered. As such, uptake in this population is subject to considerable uncertainty. If uptake is much lower than predicted, the benefits of vaccination, in terms of cases and hospital discharges averted, will be lower than those estimated.

Nirsevimab, like palivizumab, is a monoclonal antibody, and thus it is likely that offering immunisation with nirsevimab in place of palivizumab would be acceptable to the infant population who are at increased risk of severe LRTD and already eligible for or receiving palivizumab. It is more difficult to predict the acceptability and the uptake of nirsevimab in the general infant population, when presently no other monoclonal antibodies are offered to this cohort as part of an immunisation programme. Additionally, while nirsevimab has been authorised for use in the EU/EEA since 2022 and although no notable safety concerns exist at present, it should be considered that parents and or guardians may be hesitant to consent to the immunisation of an infant with nirsevimab given it is relatively new to market.

Another assumption is that nirsevimab would be offered to the infant in the days following birth, but there may be reluctance on the part of a parent and or guardian to consent to immunisation at this early stage of life. It should be considered that infants born during the RSV season whose parents and or guardians decline nirsevimab in the early days of life may opt to consent to immunisation with nirsevimab at a later date. If this was to occur, a primary care setting such as GP practice may be the most accessible and appropriate setting for delivery. As such, consideration could be given to providing an immunisation pathway through primary care to offer a second chance of immunisation where required.

A number of additional organisational challenges were identified that may affect the feasibility of implementing an RSV immunisation programme. If immunisation is offered to the general infant population born outside of the RSV season, consideration should be given to the means by which these infants will be identified and or invited for immunisation, including any onus that this could put on primary care providers to identify and or verify eligibility prior to offering immunisation. This could place a burden on primary care providers both prior to and during appointment times, and may potentially be further hindered if a functioning IT system is not in place prior to immunisation roll-out. While at present routine primary immunisations are recorded locally in GP practices, if existing systems cannot be adapted, or a new IT system is developed which differs in interface, it should be considered that additional time may be required to document details of immunisation through multiple software systems at the same visit if immunisation with RSV is delivered concurrently with routine childhood immunisations.

Difficulties with staff recruitment and retention in both primary and secondary healthcare sectors could pose a challenge to programme implementation. In the case of an immunisation programme involving delivery of nirsevimab to eligible infants through primary care settings, it should be considered that the timing of administration may place considerable pressure on GP practices over a specific number of weeks at the commencement of the RSV season. While it has been proposed that there may be the potential to administer nirsevimab concurrently with routine childhood vaccinations (scheduled for administration at two, four and six months post-birth,[313] to reduce the requirement for extra appointments), in practice this may not be possible, and may not be optimal where the timing of these routine childhood immunisations falls either immediately prior to the proposed RSV immunisation window (for example, late August), or falls a number of weeks following the commencement of an RSV immunisation window (for example, mid-October). Where it has been proposed that a catch-up immunisation programme be delivered through primary care settings, administration fees payable may facilitate hiring temporary locum staff to alleviate the burden at the commencement of the RSV season, where demand for immunoprophylaxis may be higher. This anticipated increase in workload in early autumn could be offset by reduced GP visits related to RSV-associated illness throughout the winter period.

5.5 Conclusions

Based on the assumptions used in this costing analysis, switching from palivizumab to nirsevimab for infants aged less than one year old, or for those aged less than two years old, who are at increased risk of severe RSV disease would cost less than current care.

In the case of immunisation strategies (with either nirsevimab or the maternal vaccine) targeting the general infant population, these may result in a substantial reduction in the burden of disease in this population, as well as substantial hospital costs averted. Both immunisation strategies targeting those aged 65 years and older and those aged 75 years and older would result in a reduction in the burden of disease in these populations, and avoidance of hospital costs, but are associated with a very large cost given the size of the population.

The potential impact on health outcomes and healthcare utilisation of implementing an RSV immunisation programme is subject to considerable uncertainty. Key epidemiological parameters include immunisation coverage, likelihood of hospitalisation and ICU admission, in addition to the clinical effectiveness of the available forms of RSV prophylaxis. Key costs include the estimated costs of the technologies considered and the associated administration fees and labour costs.

Importantly, the total one-year costs of these strategies is highly dependent on assuming a favourable product unit cost. This should be a key consideration in any decision-making and in procurement negotiations with manufacturers. These cost estimates are subject to substantial uncertainty; further real-world evidence may help to reduce this uncertainty.

6 Discussion

A health technology assessment (HTA) is intended to inform evidence-based decision-making in regard to the most efficient use of resources in the healthcare system. On 18 June 2024, the Minister for Health announced the RSV Immunisation Pathfinder Programme, which is being piloted for the 2024-2025 season.[12] Through this programme, parents of babies (limited to those born from September 2024 to February 2025) will be encouraged to have their babies immunised with nirsevimab before leaving the maternity unit. The aim of this rapid HTA was to inform an interim policy decision for the following season (that is, the 2025-2026 season) on the most appropriate RSV immunisation strategy for infants and or adults in Ireland. This advice is provided in the context of the clinical recommendations previously provided by NIAC to the Department of Health. An Expert Advisory Group (EAG) comprising a broad range of key stakeholders was established to support the assessment. Following completion of this rapid HTA, a full HTA including a review of the clinical effectiveness and safety, that takes consideration of the evolving evidence base and de novo economic modelling of RSV immunisation strategies, will be undertaken to inform a longer-term policy decision regarding an RSV immunisation strategy for infants and or adults in Ireland.

Respiratory syncytial virus (RSV) is a highly contagious virus (with an R_0 of 3.0), transmitted through airborne respiratory droplets by coughing, sneezing or breathing. Primary infection with RSV can cause lower respiratory tract disease in infected individuals, with symptoms typically developing between two and eight days after infection. In healthy individuals, infection with RSV is usually self-limiting, and can be managed without medical attendance. As such, supportive care and symptomatic treatment are often the most appropriate means of treating the disease. However, RSV can cause more severe infections, such as pneumonia and bronchiolitis, which may lead to hospitalisation and could be fatal. Treatment in such cases may involve administration of IV fluids, additional oxygen, or mechanical ventilation. RSV may also exacerbate chronic health conditions, in particular respiratory and circulatory conditions. Those at highest risk of disease include:

- infants aged under six months, premature infants, children aged under two years with congenital heart and lung disease, children who are immunocompromised, and children with respiratory or neuromuscular disorders
- adults aged 65 years and older, adults with comorbidities (such as, chronic heart and lung disease), and those who are immunocompromised.

Currently in Ireland, immunoprophylaxis against RSV is not included as part of either the childhood or adult immunisation programmes.(76) Palivizumab (Synagis®), a monoclonal antibody which offers passive immunisation against RSV, is reimbursed by the Health Service Executive (HSE) in specified infant populations who are considered at high risk of serious complications of lower respiratory tract disease (LRTD) caused by RSV. Palivizumab is administered directly to the infant at monthly intervals, up to a maximum of five doses.

6.1 Interpretation of the findings of the rapid HTA

6.1.1 Description of technology

Currently, there are two forms of passive immunisation for infants against RSV and two forms of active immunisation for adults aged 60 years and older that have been authorised by the European Medicines Agency (EMA) in Europe. Considering infants first, a long-acting monoclonal antibody, nirsevimab (Beyfortus®), was authorised for use in neonates and infants in October 2022. Nirsevimab is administered to the infant directly by intramuscular injection, with a single dose sufficient to infer protection against RSV for that season. In August 2023, a recombinant bivalent vaccine RSVpreF (Abrysvo®) was authorised for use in pregnant women between weeks 24 and 36 of gestation. RSVpreF provides protection to infants through transplacental antibody transfer from the mother. RSVpreF (Abrysvo®) is also authorised for adults aged 60 years and older for the prevention of LRTD caused by RSV. In June 2023, a recombinant adjuvanted vaccine RSVPreF3 (Arexvy®) was also authorised for the active immunisation of adults aged 60 years and older. It is important to note that each of these three authorised health products against RSV are currently black-triangle labelled by the EMA, meaning they are subject to additional monitoring, as described in Chapter 2, to monitor real-life experience of the health products and ensure patient safety.(43) Multiple other RSV vaccines and monoclonal antibodies are in development or are in the process of receiving marketing authorisation — for example, mResvia®, which is a new mRNA vaccine for RSV.(56)

As described in Chapter 3, in October 2023, the National Immunisation Advisory Committee (NIAC) in Ireland published high-level clinical guidance recommending the passive immunisation of all infants in their first RSV season, with no preference between immunisation with nirsevimab or the maternal vaccine for the general infant population.(11) The aim of immunisation is to reduce the incidence of RSV and the associated burden of illness both for the infants and their families and also the healthcare system. NIAC also recommended that, when available, nirsevimab should replace palivizumab for those high-risk infants and children who are currently eligible to receive palivizumab. In April 2024, NIAC published specific recommendations in

relation to the immunisation of infants with nirsevimab for the 2024-2025 RSV season, with the inclusion of detailed implementation considerations such as the timing of immunisation for specific cohorts.[78] Nirsevimab is a long-acting monoclonal antibody that requires a single dose to be administered. As such, for infants at high risk of severe disease, replacing palivizumab with nirsevimab would mean fewer appointments required for product administration, thereby reducing the burden for the infant, the infant's caregivers and the healthcare system, and facilitating a more straightforward patient care pathway.

In October 2023, NIAC also recommended the vaccination of adults aged 65 years and older against RSV prior to the commencement of the RSV season where possible.[11] NIAC does not currently indicate a preference between the two authorised vaccines, owing to their similar efficacy and safety profiles. Immunosenescence, that is, the age-related decline of an individual's capacity to mount an immune response to infections or vaccines, is an inherent part of ageing and means that older adults are generally at an increased risk of morbidity and mortality associated with infectious diseases.[62] The addition of an RSV vaccine to the adult seasonal vaccination programme could similarly be expected to reduce both the incidence of RSV, and the associated burden of illness in older adults.

6.1.2 Review of international practice

A review of international practice was undertaken, summarising the current policies in EU/EEA countries and the UK with respect to the immunisation of infants and older adults against RSV. Overall, international policy and practice in this area is changing rapidly since the authorisation of nirsevimab and the RSV vaccines. Differences in immunisation policy were identified with respect to recommendations for, and implementation of, immunisation against RSV. Differences included the choice of intervention, the population eligible for immunisation, and the reimbursement status of the recommended intervention.

Infants and children

As described in Chapter 3, until 2023, international practice across EU/EEA countries and the UK with respect to the immunisation of infants and children against RSV was limited to offering palivizumab to those at increased risk of RSV-associated disease. However, since the authorisation of the technologies outlined in section 6.1.1, passive immunisation of infants in the general population with nirsevimab and or the maternal vaccine has become widely recommended by National Immunisation Technical Advisory Groups (NITAGs) and or HTA bodies, but not necessarily funded by the relevant Ministry for Health or equivalent body.

Aside from Ireland, five countries (Belgium,[65] France,[70] Germany,[72] Spain[90] and the UK[103]) have immunisation programmes for the general infant population planned or in place for the 2024-2025 RSV season. In Belgium,[136] Spain[95, 96] and the UK,[103] as in Ireland, these programmes will be fully funded. In France, nirsevimab will be partially funded, having previously been fully funded for the 2023-2024 RSV season, while information on funding of the maternal vaccine in France was not identified.[69] In Germany, this programme is pending adoption by the Ministry of Health, having been recommended by the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute.[72]

In each of these countries, infants born during the RSV season are eligible for immunisation, although the method of immunisation (that is, use of nirsevimab and or the maternal vaccine) varies. In the UK, infants born during the RSV season will be passively immunised against RSV through the vaccination of pregnant women.[103] In Spain[90] and Germany,[72] as in Ireland, these infants will be passively immunised against RSV with nirsevimab. In Belgium[65] and France,[70, 360] either nirsevimab or the maternal vaccine will be offered, according to the choice of parents in consultation with their healthcare providers. In cases where the pregnant woman receives the maternal vaccine less than two weeks before birth, the infant will also be eligible to receive nirsevimab. Across these countries, the immunisation programmes also varied in terms of the defined timing and duration of the RSV season. However, each of the five countries offer immunisation to all infants entering their first RSV season, irrespective of whether they were born during or outside of the RSV season. In four of these countries (Belgium, France, Germany and Spain), nirsevimab will be offered to infants who were born at the end of the previous RSV season and who are entering their first RSV season. In the UK, maternal vaccination (from 28 weeks' gestation until delivery) will be offered on a year-round basis from 1 September 2024. In Ireland, the publicly-funded pilot will offer nirsevimab to all infants born during the 2024-2025 RSV season only. These countries also varied slightly in terms of the groups to be prioritised for immunisation — for example, in the event of limited supply. However, similar to Ireland, infants at high risk of RSV-associated disease are a priority cohort to receive nirsevimab in Germany and Spain, with some variation in the criteria used to define risk status.

For infants and children at high risk of RSV-associated disease, palivizumab remains widely available and recommended across all 31 EU/EEA countries and the UK. As of 1 July 2024, palivizumab is funded fully or partially for this population in 19 of these countries, including Ireland. However, changes in practice were observed in countries that are now also offering immunisation programmes for the general infant population. For the 2024-2025 RSV season, nirsevimab will be preferentially offered in place of palivizumab for infants and children at increased risk of RSV disease in

four EU/EEA countries (that is, Belgium, France, Germany and Spain). In the UK, where maternal vaccination will be offered from 1 September 2024, infants and children at increased risk of RSV disease will still be offered passive immunisation with palivizumab, regardless of whether the mother was vaccinated during pregnancy. Regarding maternal vaccination, in June 2024 the ACIP concluded that those who have received the maternal vaccine during a previous pregnancy are not recommended to receive additional doses during future pregnancies; instead, their infant should receive nirsevimab.[108] The ACIP noted that this recommendation was based on data from older adult cohorts whereby revaccination did not restore antibody levels to previous levels, and it may be updated in the future if additional data are available.

Older adults

Other than Ireland, three additional countries (France,[139] Germany[140] and Spain)[122, 142] were identified as being in the process of conducting assessments of vaccination against RSV in older adults.

While recommendations for the immunisation of older adults were identified for six countries, the presence of a high-level recommendation supporting the use of RSV vaccines does not necessarily mean that such vaccines are available, implemented as part of an immunisation programme, or funded. As outlined in Chapter 3, two countries (the UK and Czech Republic) were identified to fully or partially fund RSV vaccines for older adults for the 2024-2025 RSV season. In the UK, a publicly-funded programme offering once-off vaccination for all adults aged 75 to 79 years will be implemented from September 2024.[103] In the Czech Republic, RSV vaccines are available on an individual basis for adults aged 60 years and older and are partially funded through insurance for those aged 60 years and older, though this is not part of an immunisation programme.[138]

Overall evidence

International practice with respect to the immunisation of infants and older adults against RSV is a rapidly changing area. During 2023, the clinical evidence base consisted of clinical efficacy and safety evidence from phase 1/2 and phase 3 industry-sponsored clinical trials, as described in Chapter 3, that informed the authorisation of these products. For the 2023-2024 RSV season, the recommendations published in several countries were noted to be temporary, with decisions to inform subsequent RSV seasons expected to be made after assessing the latest available evidence. As such, it is likely that new and updated national recommendations will be developed for the 2024-2025 and subsequent RSV

seasons, as further evidence in relation to the widespread implementation of RSV immunisation becomes available.

Differences were noted among countries in terms of decision-making processes. For some countries, recommendations with respect to immunisation policy were made by National Immunisation Technical Advisory Groups (NITAGs) based on the clinical burden and evidence of effectiveness and safety. Some NITAGs also explicitly considered cost-effectiveness considerations in their decision-making. In other countries, however, economic considerations were informed by advice from HTA bodies. Policy decisions regarding funding may be automatic following a positive recommendation from a NITAG or HTA body, or it may the case that, as in Ireland, the final decision is made by the Minister for Health or representative body. Internationally, decision-making regarding RSV immunisation is further complicated since the monoclonal antibodies (that is, nirsevimab and palivizumab), are not vaccines. The remit of some NITAGs is limited to vaccines, with responsibilities for funding of non-vaccine medicinal products, such as monoclonal antibodies, lying with other agencies.

Recently, evidence has been published on the effectiveness of immunisation against RSV from countries that implemented programmes or pilots for the 2023-2024 RSV season. Seven publications from three countries (four from Spain, one from Luxembourg and two from France) have been identified as of 1 July 2024.[94, 244, 312, 324, 361, 362]

In Luxembourg, data from the 2023-2024 RSV season immunisation programme using nirsevimab demonstrated good acceptability of the intervention (84% coverage (ranging from 66% to 94%) in maternity wards) and a 69% decrease in the number of infants aged under six months being hospitalised with a laboratory-confirmed RSV infection.[80] These data informed updated recommendations by the Conseil Supérieur Des Maladies Infectieuses (CSMI) that were published in April 2024 for the 2024-2025 RSV season, as described in Chapter 3.

For Spain, four studies (published during 2024) reported on the results of immunisation programmes during the 2023-2024 RSV season.[94, 312, 324, 362] The findings from these reports were largely similar in supporting the effectiveness of nirsevimab against RSV. The most recent of these studies, published in June 2024, reported on results from a retrospective cohort study in Catalonia, covering the period between 1 October 2023 and 31 January 2024.[324] This study reported on the effectiveness of nirsevimab against RSV in infants aged less than six months. Immunisation coverage was 87.2% (n=23,127/26,525 infants). Nirsevimab was reported to be effective against RSV-associated hospital admissions (87.6% (95% CI: 82.1 to 91.4)) and against RSV-associated ICU admissions (90.1% (9%% CI:

76.3 to 95.9)). As described in Chapter 3, the Ministry of Health in Spain updated their recommendations for the 2024-2025 RSV season, based on the emerging evidence from the 2023-2024 RSV season's immunisation programme.

For France, two preprints of studies on the effectiveness of nirsevimab during the 2023-2024 RSV season were made available in the online national open archive HAL.[244, 361] One study modelled the impact of nirsevimab on hospitalisations for RSV-associated bronchiolitis following emergency room visits and estimated the number of cases averted.[361] The authors estimated that, between 15 September 2023 and 4 February 2024, nirsevimab prevented 5,800 (95% CI: 3,700 to 7,800) hospitalisations for RSV-associated bronchiolitis following emergency room visits (corresponding to a 23% (95% CI: 16 to 30) reduction compared with no administration of nirsevimab); this included 4,200 (95% CI: 2,900 to 5,600) prevented cases among those aged 0 to 2 months (corresponding to a 35% (95% CI: 25 to 44) reduction compared with no administration of nirsevimab). The second study estimated the effectiveness of nirsevimab against severe cases of RSV bronchiolitis in France, between 15 September 2023 and 31 January 2024, using surveillance data from a network of 20 volunteer paediatric ICUs (PICU).[244] Based on data for 288 infants (238 cases and 50 controls) hospitalised in 20 PICUs, the effectiveness of nirsevimab against cases of RSV-associated bronchiolitis hospitalisations with PICU admission was estimated at 75.9% (95% CI: 48.5 to 88.7). These results add to the emerging evidence base for nirsevimab, but should be cautiously interpreted, given the small sample size of the study population, especially the small control group.

While estimates from national immunisation programmes have recently been published for the passive immunisation against RSV using nirsevimab, similar evidence has not yet been identified for maternal vaccination to protect against RSV in infants. For the maternal vaccine, the clinical efficacy and safety evidence was derived from one industry-sponsored RCT.[125] The maternal vaccine was considered likely to be effective at preventing medically attended RSV-associated LRTD and RSV-associated LRTD hospitalisations in infants. However, countries noted concerns about the absence of data on RSV-related mortality, and uncertainty regarding the potential effect of the maternal vaccine at reducing ICU admissions. In the Netherlands, the Standing Committee on Vaccinations suggested that maternal vaccination may be less effective for infants born after the RSV season, as after six months the efficacy of the vaccine decreases against RSV infection requiring medical attendance and against hospitalisation due to RSV infection.[121] There were also concerns regarding the potential association between maternal vaccination against RSV and risk of preterm births, and that the MATISSE trial may not have been sufficiently powered to detect a significant increase in preterm births.[11, 121] In the

context of this risk, France and the US advise a restricted administration window between 32 and 36 wGA and Belgium recommends a preferential administration window between 28 and 36 wGA, instead of the administration window authorised by the EMA of between 24 and 36 wGA.[65] During 2024, two systematic reviews were identified that assessed the efficacy and safety of maternal RSV vaccination for preventing RSV disease in infants.[363] These reviews reported on phase 2 and phase 3 studies involving any RSV maternal vaccine, including evidence from vaccines that are currently not authorised. One review, published in January 2024, that included studies up to 1 May 2023, reported that the incidence of medically attended RSV-associated LRTD was significantly lower in the vaccine group compared with the placebo group (risk ratio (RR): 0.64 (95% CI: 0.43 to 0.96) based on four studies reporting on three RCTs (n=16,534 infants)).[363] The protective effect for the vaccine group compared with the placebo group was demonstrated up to 150 days after birth in two RCTs (RR: 0.40 (95% CI: 0.20 to 0.49); n=11,502 infants). A Cochrane review, published in May 2024, that included studies published up to 27 July 2023, concluded that maternal RSV vaccination reduced laboratory-confirmed RSV hospitalisations in infants (RR: 0.50 (95% CI 0.31 to 0.82)) based on pooled estimates from four RCTs (n=12,216 infants) with a high certainty of evidence. While the authors concluded that no safety concerns were identified for intrauterine growth restriction and congenital abnormalities, the evidence for other safety outcomes was noted to be of very low certainty.

Likewise, no estimates from immunisation programmes were identified for the immunisation of older adults against RSV through vaccination. Based on the currently available clinical and safety evidence from phase 1/2 and phase 3 industry-sponsored trials, both licensed vaccines were considered to have acceptable safety profiles regarding serious adverse events by the National Center for Immunization and Respiratory Diseases (NCIRD) in the US.[153, 162] However, the certainty of evidence relating to inflammatory neurologic events could not be assessed for RSVPreF3 (Arexvy®) and was deemed to be of low certainty for RSVpreF (Abrysvo®). A systematic review published in May 2024 reported on the efficacy of RSV vaccination to prevent LRTD in older adults.[364] The authors concluded that vaccination is effective in preventing RSV-associated LRTD in older adults, particularly in preventing severe cases with three or more symptoms, but efficacy decreases in the second season after vaccination. Limitations of the identified literature include lack of statistical power within studies for outcomes (such as hospitalisations and severe complications, including death) in older adults. An additional concern was the failure to adopt a uniform and appropriate case definition across identified studies. A number of countries have noted in their national recommendations that further safety data based on post-marketing surveillance are needed.[11, 135, 143, 147] Results of an additional industry-sponsored trial of RSVPreF3

(Arexvy®) were published in January 2024, and were therefore not available to inform assessments by countries for the 2023-2024 RSV season.[365] This phase 3 trial evaluated the immunogenicity, reactogenicity and safety of the vaccine in adults aged 60 years and older when co-administered with a seasonal quadrivalent influenza vaccine (Co-Ad group) or given 30 days apart (SA group). Reported adverse events in both groups were mild to moderate, with pain noted as the most frequent adverse event. In 12 participants (Co-Ad n=4; SA n=8) a serious adverse event with a fatal outcome was reported, although none were considered related to the investigational vaccines. As such, these findings may inform implementation considerations regarding immunisation programmes for older adults, since co-administration may enhance vaccine uptake and reduce the number of healthcare visits required for older adults to avail of both seasonal influenza and RSV vaccines.

The acceptability and feasibility of implementing an immunisation programme against RSV in infants and or older adults are important considerations.[11] Initial reports from the immunisation campaigns during the 2023-2024 RSV season from Luxembourg and Spain indicated good acceptability of nirsevimab according to the coverage achieved (approximately 84% and 92%, respectively).[82, 90] In addition, surveys assessing acceptability in Spain and France, which were carried out among healthcare professionals and parents, are expected during 2024.[70, 90] In September 2023, a survey of parental knowledge and awareness of RSV, bronchiolitis and nirsevimab was conducted in Spain prior to the start of the 2023-2024 immunisation campaign.[366] A total of 3,457 (12.5%) of parents or guardians responded. While the majority were aware of bronchiolitis (95.8%), less than half knew about RSV (46.6%). Only 11.2% of respondents were aware of nirsevimab. The authors concluded that better and more efficient educational strategies were needed to be directed towards parents and legal guardians.

As evidence continues to emerge from other countries that have started implementing immunisation programmes against RSV for infants and or older adults, updated findings from these countries may help to inform perceptions towards immunisation with these health products among healthcare providers and patients.

6.1.3 Epidemiology and burden of disease

RSV incidence data (for children aged 0 to 4 years and adults aged 65 years and older) were sourced from the Health Protection Surveillance Centre (HPSC) in Ireland (for 2013 to 2023). Hospital utilisation data were also sourced from the Hospital In-Patient Enquiry (HIPE) system (for 2013 to 2022) for both cohorts. For children aged from 0 to 4 years, acute bronchiolitis hospital utilisation data were also sourced from HIPE for the same period. It is noteworthy that HPSC and HIPE data show that, excluding 2020, there has been substantial year-on-year variability in the

burden associated with RSV in children aged 0 to 4 years and adults aged 65 years and older since 2013. Nevertheless, in general, there is a trend of increased incidence of notified RSV cases and RSV-related hospital admissions over time. In 2023, HPSC data showed that the rate of notified RSV cases in children aged 0 to 4 years was 1,699.6 cases per 100,000 population (n=5,021). When disaggregated by age group, 67% of this burden was reported in those aged less than one year, 25% in those aged 1 to 2 years and 8% in those aged 3 to 4 years; this corresponded to a case rate per 100,000 of 4,910.4 (n=2,838), 1,331.0 (n=1,539) and 527.9 (n=644), respectively. HIPE data showed that, in 2022, the total annual cost of inpatient bed days for those with a primary diagnosis of RSV was estimated at €17.5 million (for those without an ICU stay) and €5.1 million (for those with an ICU stay) in children aged 0 to 4 years. In the same year, the total annual cost of inpatient bed days for those with a primary diagnosis of RSV was estimated at €1.3 million (for those without an ICU stay) and €0.4 million (for those with an ICU stay) in those aged 65 years and older. However, these cost estimates are likely an underestimate as not all RSV cases are laboratory confirmed and some discharges may not be coded. The costs reported for Ireland were not available further disaggregated by age group. As such, it is unclear what proportion of these costs related to infants aged less than one year; though hospital utilisation data show that the largest proportion of discharges occurred in this cohort. In a study conducted in the Netherlands, data from September 2021 to June 2023 showed that the total RSV-related healthcare costs in paediatric ICUs (PICUs) ranged from €3.1 to €3.8 million per RSV season. The median per patient costs were similar for infants aged less than six months and infants aged more than six months at admission to PICUs. However, the median per patient costs were significantly higher in: infants aged less than three months compared with infants aged more than three months (€14,568.54 versus €12,253.75); infants with comorbidities compared to infants without comorbidities (€15,430.48 versus €14,186.90); and preterm infants compared to term infants (€16,501.69 versus € 14,356.85).[287]

As reported in Chapter 4, a survey of respiratory virus testing capacity and practices in acute hospital settings in Ireland (published in 2023)[294] reported that there has been an almost three-fold increase in testing capacity compared with results of the previous survey conducted in 2016 (unpublished data). The authors concluded that this expansion in testing capacity was almost certainly driven by the COVID-19 pandemic. As such, the trend of increasing incidence may be an artefact of increased surveillance and testing; if so, then the most recent data are likely a more accurate reflection of the true burden of RSV on the healthcare system. This expansion in testing capacity has been reported internationally as a result of the COVID-19 pandemic. During the COVID-19 pandemic, there was an unprecedented demand for real-time surveillance data to inform decision-making regarding pandemic

management.[367] However, it was evident that many respiratory surveillance systems lacked the required surge capacity.[368] As such, researchers and those with expertise in RSV epidemiology, virology and public health have made recommendations regarding RSV surveillance in the EU/EEA. Such recommendations included: investment in digitalisation and making use of electronic patient records; development of legislation and guidelines for case-based data sharing and data linkage; and recording of key data elements in all respiratory surveillance including symptoms and patient information (for example, age, sex, risk status, vaccination status).[368]

Similar to the pattern seen with the rates of notified RSV cases, rates of RSV-related hospitalisations and RSV ED visits were also highest among infants aged less than one year, compared with children aged 1 to 2 years, and 3 to 4 years. A lack of previous exposure to RSV, and therefore inadequate immunity, may contribute to the increased RSV incidence in those aged less than one year.[268] It is important to note that these surveillance data likely underestimate the true burden of RSV in the community. In a survey of respiratory virus testing capacity in 2023, 93% of laboratories reported testing specimens from hospital inpatients and ICU patients, whereas only 30% of laboratory-tested specimens were submitted from primary care practices.[294] There is also currently a lack of data on the wider burden of RSV in Ireland and internationally. The limited international data available report that hospitalisation of a child negatively impacts parents' and or carers' health-related quality of life, job productivity and family health and functioning.[203] Similarly, in older adults, RSV has been reported to negatively impact the daily activities, productivity, social activities, relationships and employment of those infected.[209]

In the Northern Hemisphere, the RSV season commences in September and can continue through the April the following year. In temperate regions, RSV activity generally peaks during the winter months, typically between December and January, although peaks can occur earlier.[22] As such, in a single RSV season, the majority of the burden occurs in quarter four of one calendar year and quarter one of the next calendar year. In this assessment, data relating to the incidence of notified RSV cases in children aged 0 to 4 years were reported by month and by calendar year, and HIPE data for infants aged 0 to 4 years with a primary diagnosis of RSV were reported by quarter and calendar year. In terms of monthly notified RSV cases, November, December and January tended to have the highest number of cases until the 2021-2022 RSV season onwards when October, November and December were the months with the highest number of cases reported. From 2021 to 2023, November was the month with the highest number of notified RSV cases for children aged 0 to 4 years. In terms of hospital discharges for children with RSV, quarter 4 (October to December) consistently recorded the majority of hospital discharges

both with and without an ICU stay. The number of hospital discharges, with and without an ICU stay, was highest for infants aged less than one year. This is reflected in other European countries.[196] Routinely collected hospital data from Finland, Denmark, Norway, Scotland, England, the Netherlands, and Italy (for the period 2001 to 2018) show that infants aged less than one year account for 70% to 89% of RSV-associated hospital bed days in children aged less than five years. When considering the average annual number of bed days due to RSV per 1,000 population, this was 10 to 65 times higher in infants aged less than one year when compared to children aged one to four years across these seven countries. This highlights the substantial RSV burden among infants.[196]

When compared with children, the burden of RSV in adults aged 65 years and older is substantially lower. Considering the year 2023, the RSV notified case rate was 182.1 per 100,000 (n=1,414) in those aged 65 years and older. This ranged from 99.1 cases per 100,000 (n=236) in those aged 65 to 69 years, to 464.2 cases per 100,000 (n=392) in those aged 85 years and older. Similarly, in a multi-country, observational cohort study that estimated the incidence and severity of RSV infection in community-dwelling older adults, it was reported that, although RSV is prevalent in community-dwelling older adults, it rarely causes severe disease. The authors concluded that watchful waiting and continuity of care to identify those who require more intensive care is often justified in this cohort.[369] However, it is important to note that RSV infection may be underdiagnosed in adults as they present later, the symptoms may be atypical, and they are less likely to test positive for RSV due to lower viral titres and lower yields on routine diagnostic testing.[370]

Like the paediatric cohort, the older adult cohort are not homogenous with respect to the distribution of burden associated with RSV. In addition to the notified case rate being highest in those aged 85 years and older, the rates of RSV-related hospital admissions and RSV ED visits were also highest in this age group. Moreover, the population group aged 80 years and older accounted for nearly half of hospital discharges in adults aged 65 years and older with a primary diagnosis of RSV. There is limited literature currently available regarding the burden of RSV in older adults.[275] However, a 2023 analysis of RSV-associated hospitalisation in adults aged 18 years and older estimated that, across six EU countries between 2006 and 2017, adults aged 85 years and older displayed the highest rate of RSV-associated hospital admissions.[200] Additionally, the authors estimated that 39% of the annual number of RSV-associated hospitalisations in the EU during this same period occurred in adults aged 65 years and older.[200] In Ireland, according to the HIPE data analysed for this HTA, infants aged less than one year displayed the greatest burden of RSV when compared to all of the age bands investigated, including disaggregated age bands in adults aged 65 years and older.

Hospital utilisation data from HIPE also showed that RSV is more commonly reported as a primary diagnosis in infants aged 0 to 4 years (that is, the first or principal diagnosis), whereas in adults aged 65 years and older it is more likely to be reported as a secondary diagnosis (that is, one of a number of subsequent diagnoses). Multimorbidity (that is, the presence of two or more long-term health conditions) is common among adults aged 65 years and older, with estimates that 65% of those aged 65 to 85 years, and 82% of those aged 85 years and older, have multimorbidity.[371] It may be the case that older adults are more likely to be admitted to hospital with a diagnosis other than RSV (for example, related to an exacerbation of one of their chronic conditions), and thereafter RSV is diagnosed during their hospital stay. Multimorbidity places these individuals at an even higher risk of complications following respiratory virus infection, such as RSV. In a systematic review and meta-analysis of the incidence, hospital admission rate, and in-hospital case fatality ratio associated with RSV-acute respiratory infections (ARI) in adults with comorbidity, the annual incidence rate of RSV-ARI in adults with any comorbidity was 37.6 (95% CI 20.1 to 70.3) per 1,000 persons per year in industrialised countries. While pooled data from studies using univariable analysis suggested that individuals with any comorbidity were significantly more likely to experience RSV-ARI compared with those without any comorbidity (OR 4.1, 95% CI 1.6 to 10.4) when the data were limited to studies using multivariate analysis, the association was not statistically significant (OR 1.1, 95% CI 0.6 to 1.8).[372] It is also worth noting that the population group aged 80 years and older is set to rise dramatically in Ireland, with projections estimating an almost four-fold increase in the number of individuals aged 80 years and older within the next 30 years (from 147,800 in 2016 to 549,000 in 2051).[291] This will significantly challenge the Irish healthcare system as it aims to manage this increase in older people presenting with complex combinations of chronic conditions along with acute health events.[292]

For both age cohorts, the reported Irish data on morbidity and mortality are not linked to immunisation uptake data, nor do these data give an indication of an individual's clinical risk status or presence of chronic conditions. Therefore, for infants, it is not known what proportion of the observed morbidity and mortality occurred in those at higher risk of severe RSV-related disease — that is, the group already eligible to receive palivizumab prophylaxis. For older adults, the observed morbidity and mortality occurred in a population known to be unvaccinated against RSV. While the risk status (that is, the presence of clinical conditions that increase their risk of severe disease) of these older adults is unknown, as reported already, data show that this population are more likely to be living with multimorbidity and are therefore at increased risk of complications.[371] It is also worth noting that infants are also at risk of complications. Published evidence indicates an association between infant RSV occurrence and further respiratory conditions, such as asthma,

when they get older.[273, 274] The Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure (INSPIRE) study reported that infants not infected with RSV during their first year of life have a substantially reduced risk of developing childhood asthma (adjusted Risk Ration: 0.74 (95% CI: 0.58 to 0.94), p = 0.014) compared with infants who have had an RSV infection in their first year of life. This highlights the importance of early intervention to prevent RSV in this age group.[29] Additionally, while specified groups of infants are identified as being at increased risk of severe disease associated with RSV infection (and therefore are currently eligible for palivizumab prophylaxis), the evidence base relating to risk factors associated with poor outcomes in children is limited by a paucity of standardised data.[373] This reinforces the need for improved surveillance data and data linkage relating to infectious respiratory diseases.[172]

Currently in Ireland, there are no national immunisation programmes against RSV for children and or older adults. For both cohorts, the potential acceptance and uptake of immunisation against RSV is unknown, although expectations and insights may be informed using other existing immunisation programmes. Palivizumab is currently only available to specific groups of infants and children who are deemed to be at high risk of severe RSV disease. While uptake rates among this eligible population are not known, Primary Care Reimbursement Scheme data (from 2019 to 2023) report that the number of children who have accessed palivizumab in primary care has ranged from 627 in 2021 to 768 in 2019. Currently, the earliest immunisation of infants occurs at two months of age. HPSC data for the period 2018 to 2022 indicate that uptake of the primary immunisation schedule (all vaccines) in infants aged up to 12 months has ranged from 87.2% to 90.0%. However, these data may not reflect uptake of a novel immunisation technology for infants aged less than two months in Ireland.

In March 2023, Galicia (Spain) was one of the first regions worldwide to incorporate nirsevimab into its immunisation programme for RSV prophylaxis in infants. The 2023-2024 immunisation campaign with nirsevimab, which commenced on 25 September 2023 and concluded on 31 March 2024, targeted infants born during the season, infants aged less than six months at the start of the season, and infants aged 6 to 24 months at risk of severe disease related to RSV.[86, 374] The NIRSE-GAL longitudinal population-based study in Galicia aimed to assess the effectiveness of nirsevimab in preventing hospitalisations during the 2023-2024 immunisation campaign.[92] Initial results from the study showed that nirsevimab was highly accepted, with more than 90% of eligible infants being immunised within three months of the campaign launch.[312] The authors reported that this high uptake was driven by various factors relating to its implementation, including: a robust information and education campaign, hospital-based roll-out for those born during

the season; a flexible electronic appointment system (which included weekends) for those aged less than six months at the start of the season; and utilisation of the network of primary care paediatricians to capture those who missed their immunisation appointment.[312]

There are very limited nationally collected data relating to uptake of vaccines routinely offered to pregnant women. However, World Health Organization (WHO) influenza vaccination coverage data indicate that 62% of pregnant women in Ireland received an influenza vaccination in 2018; though this decreased to 42% in 2020.[301] Additionally, a 2024 ECDC report on COVID-19 vaccination coverage during the 2023-2024 season reported that 19.6% of pregnant women in Ireland received a single dose of a COVID-19 vaccine between September 2023 and March 2024.[227] However, the motivation for accepting a vaccine during pregnancy may differ depending on the aim of the vaccine offered. For example, influenza and COVID-19 vaccines are primarily aimed at protecting the mother.[231] However, in the case of the pertussis vaccine, similar to the maternal RSV vaccine, the primary aim is to protect the newborn baby in the first few months of life.[232] While pregnant women can also become sick with whooping cough, the risk of severe infection and death is much greater in newborns.[233] This aim to protect the baby has been reported to be a strong motivation for vaccine uptake in pregnant women.[231] A 2024 study, exploring potential factors influencing parental decision-making towards RSV immunisation options, compared maternal pertussis vaccination uptake in pregnancy with infant vaccination in the same year. In 2022, for England and Spain (the two countries for which national data were available), maternal pertussis vaccination uptake was 64% and 86%, respectively; whereas infant pertussis vaccination uptake for both countries was 93%.[375]

Ireland-specific data from a survey conducted in one maternity hospital (in 2018 and 2019) reported that, of the 528 women surveyed, 48.5% would accept an RSV vaccine, if available, and 45.8% were undecided.[302] Factors associated with increased acceptance were feeling confident in recommended vaccines and that these vaccines would protect their baby from illness. Awareness of RSV was low among the women surveyed, with only 9.5% of respondents reporting knowledge of the significance of RSV in infancy. However, it is likely that awareness of RSV among pregnant women in Ireland has increased since the time of data collection, given the trend of increasing incidence of RSV and RSV-related hospital admissions over time. Additionally, a 2023 scoping review reported on the reasons for, and approaches to, non-uptake of pertussis and influenza vaccinations in pregnant women in the UK and Ireland. Overall, the findings of the review highlighted that pregnant women need clear, comprehensible information, ideally provided by their healthcare professionals, in a way that is meaningful and addresses their circumstances and attitudes.[234]

Similarly, in the absence of an established RSV vaccination programme for older adults, uptake data in relation to the HSE's existing seasonal influenza and COVID-19 vaccination programmes may be relevant indicators of potential RSV vaccine uptake. In adults aged 65 years and older, uptake of the seasonal influenza vaccination was 76.5% (for the 2022-2023 season). While uptake of the primary course and first booster of the COVID-19 vaccine was high at 99.4% and 95.7%, respectively, uptake of the 2023-2024 autumn booster dropped to 56.5%. In a systematic review of the barriers and attitudes towards influenza vaccine uptake in those aged 18 to 64 years,[376] the barrier most frequently agreed upon was a perception of a lack of knowledge about the vaccine. Trust in healthcare services was the most agreed upon promoter for influenza vaccine uptake. Another systematic review synthesised qualitative evidence on healthcare workers' perceptions and experiences of seasonal influenza vaccination.[377] The authors reported several barriers to vaccine uptake, such as concerns about side-effects, doubtfulness regarding vaccine effectiveness, and the belief that influenza is not a serious illness.[377] The authors of both reviews concluded that strategies to encourage uptake should be directed towards creating a better understanding of vaccines and their value through education.[376, 377] Similarly, guidance from the WHO suggests that improved uptake of public health interventions such as influenza vaccination can be facilitated by consistent and targeted information delivered through trusted channels of communication.[378]

6.1.4 Costing analysis

A costing analysis was performed to estimate the potential cost and benefits associated with introducing an RSV immunisation programme in Ireland for the 2025-2026 season, specifically considering strategies involving the passive immunisation of children (through use of either a directly acting monoclonal antibody or maternal vaccination), and strategies involving the active immunisation of older adults. In addition to providing an estimation of programme costs, organisational challenges associated with these strategies were also outlined. All passive immunisation strategies targeting the paediatric populations were compared against the existing standard of care, that is, palivizumab, a short-acting monoclonal antibody offered at monthly intervals (for up to five doses) to those children considered to be at increased risk of severe RSV disease. In the case of active immunisation of adults aged 65 years and older, RSVpreF and RSVPreF3 were compared against the current standard of care, that is, no immunisation. In the base-case analyses, assumed unit costs of the technologies under assessment were €301.12 in the case of nirsevimab, and €165 in the case of both RSVpreF and RSVPreF3.

The costing analysis found that for children at increased risk of severe disease who are currently eligible for palivizumab, switching to nirsevimab would cost less than current care, at the assumed base case unit cost of nirsevimab. This was found to be true in the case of both estimated paediatric populations — that is, infants aged less than one year and children aged less than two years — and was determined to be robust to the range of unit costs of nirsevimab assessed. If RSV immunisation was limited to this population at increased risk, the eligible children would be easily identifiable, as invitation for immunisation would be issued by a specialist prescriber, as is currently the case for palivizumab. From an organisational perspective, switching from a short-acting monoclonal antibody administered monthly to a long-acting monoclonal antibody administered as a single dose would be efficient, and may ensure more complete protection throughout the RSV season. Assuming nirsevimab is administered through a secondary care setting, it is anticipated that there would be no undue disruption or burden over and above the current standard of care. It was assumed that there would be no programme costs incurred by the National Immunisation Office (NIO) if RSV immunisation was limited to this population at increased risk given that systems are already in place to administer palivizumab to this cohort.

Two technologies were assessed in strategies involving the passive immunisation of the general infant population (that is, those infants not deemed to be at increased risk of severe RSV), specifically nirsevimab administered directly to infants, and the maternal vaccine (that is, RSVpreF) administered to pregnant women due to have their baby during the RSV season. At the assumed product unit costs, expanding RSV immunisation to the general infant population was estimated to result in an incremental cost to the HSE ranging from €2.54 million (95% CI: -€1.17 to €6.80 million) to €5.45 million (95% CI: -€1.96 to €13.97 million) for strategies involving nirsevimab administration, while the cost associated with the maternal vaccine were estimated to be broadly comparable to the hospitalisation cost offsets for this strategy (estimated incremental cost €0.01 million (95% CI: -€2.24 million to €2.43 million)). These variable cost estimates do not consider the substantial fixed costs associated with the implementation of a new RSV programme, which are estimated to be approximately €2.3 million regardless of uptake rates. The costs associated with implementation of a new RSV immunisation programme included a public health information campaign, appointment of programme administrator, development of training materials, IT system management, and additional storage and distribution requirements. All strategies were estimated to result in substantial hospital costs averted in the infant cohort, though the impact of the maternal immunisation strategy was estimated to be lower compared with nirsevimab-based strategies for those born within the RSV season.

If immunisation with nirsevimab was to be offered to infants born during the RSV season (for example, those born from September to February), it was proposed that immunisation would be offered in the days after birth, ideally during the routine clinical assessment conducted by midwives in a maternity unit and or hospital. From an organisational perspective, distribution of births can vary markedly across the existing 19 maternity units and hospitals in Ireland. Consequently, delivering immunisation on wards could place a substantial seasonal burden on existing staff capacity given the aim to maximise uptake within a short time frame prior to the anticipated start of the RSV season. If staffing capacity throughout the RSV season was adequate to allow for immunisation in maternity units and hospitals during the routine clinical assessment, this would likely bolster immunisation uptake in this infant cohort, as has been observed in the 2023-2024 season in Galicia, Spain.[312]

Offering immunisation in the days following birth facilitates the best chance of ensuring protection as immunity can take up to two weeks to develop post-immunisation. It is possible that a new parent and or guardian may be hesitant to consent to immunisation of their newborn infant in the days after birth, whether due to perceived safety concerns regarding nirsevimab or immunisation more generally, lack of information at the time of consent, or simply due to parental preference. It is also possible that, while an initial offer of immunisation for the infant may be declined at this early stage of life, a parent and or guardian may then reconsider and subsequently opt for immunisation for an eligible infant at a later date. Therefore, it is equally important that consideration is given to the most appropriate setting by which a second chance of immunisation might be offered in this circumstance. While from an organisational perspective, it may be more straightforward to facilitate this second chance of immunisation through a hospital setting, it should be considered that this could introduce a further element of unpredictability and burden on secondary care. As such, this second chance of immunisation may be best facilitated through primary care (that is, through GPs and or practice nurses).

Key challenges regarding the immunisation of infants born outside of the RSV season (that is, those considered to be part of a catch-up cohort), include the means by which this cohort are invited for immunisation, the location of immunisation delivery and the management of this additional burden. Organisationally, infants who fall into this cohort first need to be identified as eligible and invited for immunisation. For the purposes of costing the delivery of immunisation to a catch-up infant cohort, it was proposed that these infants may be offered immunisation through primary care, delivered by their GP or practice nurse. However, it may be challenging for primary care contractors to identify eligible infants in advance of the RSV season. Additionally, any appointment scheduling and rescheduling would fall on the contractor, or their administrative staff. Moreover, the goal of RSV

immunisation is to achieve maximum uptake prior to the RSV season. If immunisation was offered to all infants entering their first RSV season, this would mean a sizeable population (comprising almost 28,000 infants in the catch-up cohort) would need to be immunised over a brief period (of up to two months). Furthermore, while there may be an opportunity to offer immunisation to eligible infants alongside routine primary childhood immunisations, this will not be the case for all infants, and as such, there would be pressure on primary care contractors to schedule additional appointments for these infants. If immunisation was to be offered to a catch-up infant cohort through a GP setting, appropriate supports would need to be in place to ensure that immunisation of this sizeable infant cohort can be executed.

While the costs associated with delivering a maternal immunisation strategy were estimated to be broadly comparable to the hospitalisation cost offsets for this strategy, it was also estimated that there would be fewer RSV-related hospital cases averted in the infant population than that for nirsevimab at the same uptake. This can be attributed both to the lower reported efficacy of the maternal vaccine[126] in comparison with nirsevimab,[109, 112, 323] and the wider confidence intervals reported for the efficacy estimate of the maternal vaccine.[126] The final results of the MATISSE RCT (when published) should provide more clarity on whether this reported efficacy for the maternal vaccine remains relatively comparable to that used in this analysis. Organisationally, it was not considered to be overly burdensome to offer maternal immunisation through the expectant mother's GP, in the same manner by which pertussis and seasonal respiratory vaccinations are currently offered, especially since the expectant mother would be attending their GP for scheduled visits within the recommended immunisation window as part of the Maternity and Infant Care Scheme. The main challenge regarding the maternal immunisation strategy is anticipating maternal immunisation uptake in Ireland. As previously outlined, there is a lack of clarity on antenatal vaccine uptake generally in Ireland, with available data limited to small cohort studies, and isolated estimates. As a result of this dearth of information, from a procurement perspective, it is challenging to put a meaningful figure on the quantity of product required, and there is a significant risk that adopting a maternal strategy could result in either over- or under-purchase of product required for the 2025-2026 season. Additionally, unlike nirsevimab,[312, 324] there are no national maternal immunisation programmes from which real-world effectiveness can be ascertained.

Aside from product and administration costs, there are significant programme costs associated with the introduction of any RSV immunisation programme (with the exception of offering nirsevimab instead of palivizumab to those at increased risk of severe RSV disease as this strategy would primarily involve a relatively

straightforward swap). As reported already, these programme costs are estimated to amount to €2.3 million. Moreover, while analysing the costs and benefits of combination strategies was considered beyond the scope of this rapid HTA, the costs of a combination strategy — that is, offering both maternal immunisation (at varying uptake rates) and nirsevimab to those infants born during the RSV season who remain unprotected — were estimated in a scenario analysis in Chapter 5. Such a strategy may offer an opportunity to offset some of the costs of procurement associated with the assumed higher unit cost of nirsevimab, but it should also be considered that offering a combination strategy may further disincentivise maternal vaccine uptake. Furthermore, a combination strategy may also result in over- or under-purchase of two products, which would likely be centrally procured in bulk prior to the RSV season. As such, there is a risk of either having insufficient product to meet demand, or storing unused product into a second RSV season.

The incremental cost of offering immunisation against RSV to adults aged 65 years and older, and adults aged 75 years and older, was estimated to be €144.9 million and €75.2 million respectively, at the assumed base case unit costs. While the substantial cost can be attributed to the cost of offering immunisation to sizeable target populations (that is, n=840,830 adults aged 65 years and older, and n=381,856 adults aged 75 years and older), the estimated secondary care costs avoided were substantially lower than those estimated for immunisation strategies targeting infants. Notably, within the older adult cohort, the analysis showed that the hospital burden associated with a primary diagnosis of RSV increases with age, with greater potential for hospital costs averted in those aged 75 years and older relative to the estimated cost of an RSV immunisation programme. It should be noted that there are two RSV vaccines authorised for use in this older adult population, RSVpreF and RSVPreF3. While a unit cost per vaccine in this analysis has been informed by the current Irish list price for RSVPreF3, there may be potential to negotiate a lower cost per unit as part of a competitive tender process given the similar vaccine efficacy reported for both products. Additionally, efficacy estimates used in this analysis were taken from ongoing phase 3 RCTs for each product, which report efficacy against RSV over one season. Vaccine manufacturers have indicated that RSV vaccines provide sustained protection into a second season for this older adult cohort, though these data are not yet published.[356, 357] It is noted that the planned immunisation strategy in the UK will offer once-off immunisation to adults turning 75 years with an initial catch-up period in 2024 for those already aged 75 to 79 years. As stated previously, this costing analysis was undertaken to inform the one-year cost of offering RSV immunisation; if, after conclusion of these RCTs, data show that annual vaccination of older adults is not required, this will impact the cost of offering vaccination to older adults if considered over a longer time period as well as the cost effectiveness of this strategy.

The results of this analysis must be taken in the context of the limitations of the data. Incidence of RSV for this analysis is based on notified cases; however, as outlined in Chapter 3, not all cases of RSV are notified, and therefore the true burden of both medically and non-medically attended cases of RSV in the community are likely underestimated. The estimated cost for the various strategies considered hospital costs averted through RSV-related hospitalisations avoided. Only hospital discharges associated with a primary diagnoses of RSV were used in this analysis. Therefore, costs of discharges associated with a secondary diagnosis of RSV were excluded when estimating the costs averted. As such, the estimated cost of each strategy should be considered conservative, though in the case of immunisation strategies targeting older adults, including costs averted from secondary diagnoses in the analysis would not be sufficient to improve the proportional costs of immunisation relative to potential costs averted.

Furthermore, the burden of RSV in infants and adults with risk factors for severe disease and or comorbidities cannot be disaggregated from those in the general population. Data used for immunisation strategies targeting infants specifically relate to those infants aged less than one year, while expert opinion provided to the EAG for this rapid HTA has advised that the majority of hospitalised cases and paediatric intensive care unit (PICU) cases occur in those aged less than four months, predominantly in Q4 of each year. International data from the Netherlands appears to support this, with the BRICK study estimating that, over two consecutive seasons, 2021-2022 and 2022-2023, the median age of an infant admitted to ICU was 45 days old and 49 days old, respectively, with the proportion of infants aged less than or equal to six months reported to be 89.8% and 92.5% respectively.[287] Moreover, the study found that significant PICU costs (between €1.9 million and €2.6 million) could be averted per RSV season through use of either maternal vaccination or nirsevimab.[287] It should be noted that, in the case of both infants and older adults, any reduction in discharges associated with RSV-related ICU admissions, however small, would ease the burden in secondary care during the winter season, through improved ICU capacity.

In this analysis, estimated costs associated with RSV-related hospital discharges averted were considered in the context of potential financial gain rather than in the context of any health benefit gained by an individual. In contrast, a full economic evaluation would assess the cost effectiveness of adopting any RSV immunisation strategy over a longer time horizon, with findings presented as an incremental cost of the technology per quality-adjusted life year gained by an individual. Following completion of this rapid HTA, a full economic evaluation will be undertaken as part of a full HTA of immunisation against RSV in Ireland, as requested by the Department of Health. This economic evaluation will aim to address some of the

limitations of the costing analysis which contribute to the uncertainty in the estimates, as outlined in Chapter 5. For example, this analysis does not consider any reduction in overall RSV transmission which may be achieved through adopting any of the strategies, and only considers the direct impact on notified cases and hospital discharges in the target populations. Use of a dynamic transmission model as part of an economic evaluation would aim to estimate the impact of any strategy at reducing overall transmission in a population. A review of published economic modelling studies will also be undertaken as part of the full HTA, to inform whether a dynamic transmission model is a necessary component in any economic evaluation conducted, in addition to informing parameters which may be included in the model.

An economic evaluation may also take into account indirect costs associated with RSV, such as the opportunity cost of productivity loss which might occur due to caregiving responsibilities, and capture any potential reduction in quality of life experienced by an infant or adult infected with RSV. Furthermore, additional data relating to the efficacy and effectiveness of the technologies under assessment may become available, following the publication of results from several studies.[42, 126, 149] Given that no national programmes in EU/EEA countries and the UK had specifically funded RSV vaccines for the 2023-2024 RSV season, there may not be any additional data relating to real-world effectiveness following their administration to maternal and older adult populations that can be used to inform the full HTA. However, further data regarding the real-world effectiveness of nirsevimab as part of national immunisation programmes may become available as several countries and regions funded nirsevimab for the 2023-2024 RSV season, as outlined in Chapter 3. All of which may better inform estimates of clinical efficacy, effectiveness and or safety as part of an economic evaluation.

Moreover, the estimated cost of the immunisation strategies is highly sensitive to cost of procurement. As previously stated in Chapter 5, while there is more certainty regarding the Irish unit cost of RSV vaccines, there is considerable uncertainty regarding the unit cost of nirsevimab. Further clarity on nirsevimab pricing across Europe may better inform an assumed base case unit cost of nirsevimab for an economic evaluation, failing an Irish list price for nirsevimab becoming available. Lastly, as outlined in Chapter 5 and above, data relating to infants in this analysis were specific to infants aged under one year, and were not further disaggregated by age. While there are issues with data suppression due to small numbers, Irish ED- and PICU-related data may become available, which may provide further granularity regarding the severity of RSV disease in infected infants, and the age at which infants are most likely to be admitted to a PICU for severe complications.

6.2 Conclusions

This rapid HTA has been conducted to support timely evidence-based decision-making relating to alternative infant and adult immunisation strategies against RSV in Ireland. Recently, two forms of passive immunisation of infants against RSV have been authorised for use in Europe, as well as two vaccines for the prevention of RSV in older adults, all subject to additional monitoring to ensure patient safety. Aside from Ireland, five European countries will offer nirsevimab and or the maternal vaccine through publicly-funded immunisation programmes that are planned or in place for the 2024-2025 RSV season. In addition, two countries (one fully and one partially funded) will offer at least one of the RSV vaccines for the immunisation of older adults against RSV, for the 2024-2025 season. Around Europe, updates and revisions to the recommendations and implementation decisions with respect to immunisation against RSV are expected during 2024 to inform subsequent RSV seasons, as evidence continues to become available for these health technologies. While the burden of RSV in infants and older adults is substantial, the largest healthcare utilisation burden was observed for infants aged less than one year. However, there is considerable uncertainty in relation to the potential impact of implementing an immunisation programme against RSV; this uncertainty primarily relates to the acquisition price and fees associated with the different forms of immunisation.

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Appendices

Appendix 3.A

Table 1 Summary of recommendations for the prevention of RSV in infants and young children, as of 1 July 2024

Country	Recommendation	Evidence underpinning recommendation	Implemented as part of an immunisation programme Funding status
Austria			
Palivizumab	Available for:[134] ▪ premature infants born <35 wGA and aged <6 months at the start of the RSV season ▪ children aged <2 years with BPD (treated within the previous six months) or HS-CHD	N/A	***Implemented as part of an immunisation programme:*** Available, but not part of an immunisation programme.[134] ***Funding status:*** Not funded as of 1 July 2024.
Nirsevimab	Approved for prevention of RSV disease in newborns, infants and young children during their first RSV season. Austrian market launch expected in 2024.	N/A	***Implemented as part of an immunisation programme:*** No ***Funding status:*** N/A
Maternal vaccine	Available for pregnant women (24 to 36 wGA) from autumn 2023. Pregnant women can choose to receive the vaccine, preferably between September and March.	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme. ***Funding status:*** Not funded as of 1 July 2024.
Belgium			
Palivizumab	Recommended and funded for high-risk children:	N/A	***Implemented as part of an***

	▪ infants born ≤28 wGA and aged <1 year at the start of the RSV season ▪ infants born 28 to <35 wGA and required >48 hours ventilation, a NICU stay and aged <6 months at the start of the RSV season ▪ infants aged <2 years at the start of the RSV season suffering from chronic respiratory failure who require chronic oxygen therapy or other ventilator support at home ▪ infants aged <2 years with HS-CHD. The Superior Health Council (SHC) recommended using palivizumab for high-risk infants for the 2023-2024 RSV season as nirsevimab is not expected to be on the market in Belgium in time.[65]		***immunisation programme:*** Yes ***Funding status:*** Eligible for full funding.[136]
Nirsevimab	Not on the market in Belgium for the 2023-2024 RSV season. Expected to be available from September 2024.[67] For the 2024-2025 RSV season, the SHC recommends, on a temporary basis, the use of nirsevimab for: ▪ all babies from unvaccinated mothers ▪ babies born prematurely (<30 wGA) ▪ babies born within two weeks following administration of the maternal vaccine. Nirsevimab should replace palivizumab for high-risk children. The SHC recommends that either nirsevimab or the maternal vaccine may be used, with the choice of product at the discretion of healthcare providers and parents.[65]	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY	***Implemented as part of an immunisation programme:*** Not yet implemented. Several potential immunisation strategies proposed by the SHC.[65] ***Funding status:*** Eligible for funding with a co-payment of between €8 and €12.10 payable by the individual.[136]
Maternal vaccine	For the 2023-2024 RSV season, the SHC supported the administration, on an individual basis, of the maternal vaccine for every woman	▪ national and international epidemiology and burden of disease	***Implemented as part of an immunisation programme:***

	expected to deliver before the end of March 2024. For the 2024-2025 RSV season, the SHC recommend, on a temporary basis, the use of the maternal vaccine for women expected to deliver between early September and end of March. The SHC recommends 28 and 36 wGA as the preferential window for vaccination. The SHC recommends that either nirsevimab or the maternal vaccine may be used, with the choice of product at the discretion of healthcare providers and parents.[65]	▪ clinical efficacy and safety trials: ○ MATISSE	No information identified. ***Funding status:*** No information identified.
Bulgaria			
Palivizumab	Recommended and administered to high-risk children from the beginning of November until early March: ▪ children aged <2 years with BPD ▪ children aged <2 years born 32 to 35 wGA ▪ can be considered in children with severe immunodeficiency and cystic fibrosis.[379]	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for full funding.[380]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Croatia			

Palivizumab	Recommended for the following groups at the start of the RSV season: ▪ Children without comorbidities born at: ○ ≤28+6 wGA and aged ≤9 months ○ ≤29+0 to 31+6 wGA and aged <6 months ○ 32+0 to 35+6 wGA and with certain risk factors. ▪ Children with BPD aged ≤1 year, or aged ≤2 years who use supplemental oxygen and or medicines such as bronchodilators, and or with pulmonary hypertension. ▪ Children aged ≤1 year with cyanotic or non-cyanotic HS-CHD, or aged ≤2 years if accompanied by haemodynamic instability. ▪ Children aged ≤1 year with Down syndrome but without CHD, based on paediatrician's risk-based recommendation. ▪ Children with CLD aged ≤2 years. ▪ All children with cystic fibrosis aged ≤1 year. ▪ Children with cystic fibrosis aged ≤2 years with severe lung disease or growth restriction. ▪ Children aged ≤2 years with NMD or diseases of the central nervous system or spine that compromise the normal function of the respiratory system and swallowing. ▪ Children aged ≤2 years with primary immunodeficiency or under cytotoxic or immunosuppressive therapy.	N/A	***Implemented as part of an immunisation programme:*** Included in the implementation programme of immunisation, seroprophylaxis and chemoprophylaxis for special population groups and individuals at increased risk of certain diseases for 2023[381] and 2024.[382] ***Funding status:*** Eligible for full funding for the recommended groups.[381, 382]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A

Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Cyprus			
Palivizumab	Recommended for:[213] ▪ infants born <29 wGA in the first year of life ▪ infants born <32 wGA with BPD (defined as requiring >21% oxygen for a minimum of 28 days after birth) in the first year of life and in the second year of life for those who continue to require medical intervention.	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme.[383] ***Funding status:*** No information identified.
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	**N/A**	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Czech Republic			
Palivizumab	Recommended for :[384] ▪ Infants born ≤31+6 wGA during the RSV season or entering their first RSV season. Infants who received immunoprophylaxis between January and March are not covered for additional doses. ▪ Infants with BPD who required treatment for CLD (oxygen therapy, bronchodilator therapy, corticoids, diuretics) 6	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme. ***Funding status:*** Full or partial funding,

	months before the start of the RSV season. These infants can receive palivizumab in their second RSV season if undergoing treatment. ▪ Infants born premature at risk of nosocomial RSV infection can be treated with 1 dose of palivizumab. ▪ Children aged <2 years with HS-CHD. ▪ Infants born 32+0 to 34+6 wGA who meet a risk score of ≥4 points based on the following: ○ chronological age less than 3 months (1 point) ○ severe neurological disease (periventricular leukomalacia, intracerebral haemorrhage, stroke, hydrocephalus) (1 point) ○ weight less than 10th percentile (1 point) ○ discharge from hospital from 1 October to 30 April (1 point) ○ older sibling (1 point) ○ child from multiple pregnancy (0.5 points) ○ movement in childcare group (0.5 points) ○ smoking in joint household (0.5 points) ○ social status/'crowding' (>5 family members living in a small space) (0.5 points).		depending on strength, for recommended groups.[384]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[385]
Maternal vaccine	Authorised and available by prescription for pregnant women	N/A	***Implemented as part of an***

	between 24 and 36 weeks' gestation.[386]		***immunisation programme:*** N/A ***Funding status:*** Not eligible for full funding as of 1 July 2024. Individual insurance companies provide partial funding.[386, 387]
Denmark			
Palivizumab	Recommended:[388, 389] ▪ during the first year of life for premature infants, born <32 wGA, with lung disease, including BPD, and with continued need for supplemental oxygen, CPAP or a ventilator at term (40 wGA) ○ can be considered during the second year of life for this cohort or if severe structural lung damage is present ▪ for those with HS-CHD or cyanotic-CHD in the first year of life and may be indicated up to 2 years of age in rare cases. Palivizumab can be considered after expert assessment in children with CLD or conditions with significant or secondary impact on the respiratory tract, such as: ▪ congenital anomalies or NMD ▪ cystic fibrosis or primary ciliary dyskinesia ▪ severe immunodeficiency with secondary structural damage.	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme.[390] ***Funding status:*** No information identified.
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A

Maternal vaccine	Available for pregnant women between 24 and 36 weeks' gestation.	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme.[391] ***Funding status:*** Not funded as of 1 July 2024.
Estonia			
Palivizumab	Recommended for children at high risk of RSV:[213, 392, 393] ▪ infants born <28 wGA and aged <1 year at the start of the RSV season. ▪ infants born between 29 and <32 wGA and aged <6 months at start of RSV season. ▪ infants born between 32 and <35 wGA, aged <3 months at the start of the RSV season and attend nursery school or have other children aged <5 years at home. For this group, RSV prophylaxis is only indicated until aged three months. ▪ children aged <1 year at the start of the RSV season and have congenital pulmonary or neuromuscular malformations. ▪ children aged <2 years with BPD who have received treatment for BPD within 6 months of the start of the RSV season. ▪ children aged <2 years at the start of the RSV season with HS-CHD and either a need for treatment for congestive heart failure, or moderate to severe pulmonary hypertension, or cyanotic heart disease.	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme.[394] ***Funding status:*** Not funded as of 1 July 2024.[395]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:***

			N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Finland			
Palivizumab	Recommended: ▪ for preterm infants born <29 wGA and aged <1 year at the start of the RSV season.	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme. ***Funding status:*** Not funded as of 1 July 2024.[396]
Nirsevimab	According to the Finnish Institute of Health and Welfare, nirsevimab is not available in Finland.[397]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	Available for pregnant women from private health care providers and pharmacies, with a doctor's prescription.[397]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[396]
France			
Palivizumab	Available for newborns and infants at high risk of RSV infection only:[119] ▪ infants born ≤35 wGA and aged <6 months at the start of the RSV season ▪ children aged <2 years who have required treatment for BPD in the last three months	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Not funded as of 1 July 2024.[398]

	▪ children aged <2 years with HS-CHD.		
Nirsevimab	Recommended and available from September 2023 for:[119] ▪ all infants entering their first RSV season (nirsevimab will be administered as a priority to those born since 6 February 2023 and then to those born from 15 September 2023, preferably before leaving the maternity ward) ▪ as an alternative to palivizumab for eligible populations.	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ organisational implications ○ impact on healthcare services ○ treatment pathway of patients	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for partial funding.[69]
Maternal vaccine	Recommended that a maternal vaccination campaign with RSVpreF (Abrysvo®) run concomitant with the 2024-2025 nirsevimab immunisation campaign, or begin in September and run until the end of January 2025.[70] The maternal vaccine can be administered to pregnant women between 32 and 36 wGA. (399)(399)(400)(400)(400)(400)(399)(399)(29)(29)(29)(29)	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ comparison with monoclonal antibodies ▪ economic evaluations ▪ acceptability of vaccination	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** No information identified.[400]
Germany			
Palivizumab	Recommended for:[401] ▪ children at high risk of severe infection aged ≤2 years at the start of the RSV season ○ who required concomitant therapeutic measures for BPD (supplemental oxygen, steroids, bronchodilators) in the last six months before	N/A	***Implemented as part of an immunisation programme:*** No ***Funding status:*** Eligible for full funding.

	the start of the RSV season ○ with HS-CHD ○ with Trisomy 21 ▪ infants born <35 wGA and aged ≤6 months at the start of the RSV season.		
Nirsevimab	In January 2024, the Federal Joint Committee amended the previously adopted Medicines Directive for palivizumab to also include nirsevimab. Nirsevimab is recommended for:[402] ▪ children at high risk of severe infection aged ≤1 year at the start of the RSV season ○ who required concomitant therapeutic measures for BPD (supplemental oxygen, steroids, bronchodilators) in the last six months before the start of the RSV season ○ with HS-CHD ○ with Trisomy 21 ▪ infants born <35 wGA and aged ≤6 months at the start of the RSV season. The recommendation is to be updated should the EMA approval of nirsevimab be extended to include "children up to 24 months of age who remain vulnerable to serious RSV disease in their second RSV season".[403] In June 2024, the EMA adopted this extension of indication request.[49] A recommendation from STIKO is not required for secondary antibody prophylaxis.[75] In June 2024, the STIKO recommended immunisation with nirsevimab for all infants, regardless of risk factors, before or during their first RSV season. Nirsevimab administration is recommended: ▪ in the autumn before the start of their first RSV season, for	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ preliminary surveillance data for the 2023-2024 RSV season for countries with nirsevimab immunisation programmes: ○ Spain ○ Luxembourg ○ the US ▪ epidemiological modelling and economic evaluation of potential immunisation strategies ▪ acceptance of nirsevimab among parents and guardians ▪ ethical considerations.[72, 118]	***Implemented as part of an immunisation programme:*** No ***Funding status:*** Eligible for full funding.

	infants born between April and September ▪ as soon as possible after birth, for infants born between October and March ▪ before discharge, for infants with a longer postnatal hospital stay, if the stay falls during the RSV season. Nirsevimab should be considered during the hospital stay to prevent nosocomial infections, if deemed appropriate. Nirsevimab is not recommended for healthy infants whose mothers received RSV vaccination during pregnancy. However, nirsevimab is recommended if maternal vaccination took place less than two weeks before birth. For infants with known risk factors, the use of palivizumab or nirsevimab must be decided on an individual basis. In case of limited supply, nirsevimab should be prioritised for infants at high risk of severe infection (as above), and infants aged <6 months. The STIKO noted that it will regularly evaluate its recommendation and adapt it, if necessary.[72]		
Maternal vaccine	In June 2024, the STIKO concluded that there are insufficient data on maternal vaccination available to decide on a possible recommendation. Once new evidence is available, STIKO will review and evaluate it again.[72]	▪ clinical efficacy and safety trials: ○ NCT04032093 ○ MATISSE	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Greece			
Palivizumab	Considered (no recommendation) for infants <35 wGA and those with BPD, CHD or SCID aged <2 years at the start of the RSV season.[63]	N/A	***Implemented as part of an immunisation programme:*** No[404] ***Funding status:*** No information identified.

Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Hungary			
Palivizumab	Recommended for:[213] ▪ infants born <36 wGA and aged ≤6 months at the start of the RSV season ▪ children aged <2 years who required treatment for BPD in the previous six months ▪ children aged <2 years with severe CHD.	N/A	***Implemented as part of an immunisation programme:*** No information identified. ***Funding status:*** Eligible for full funding if prescribed by a neonatologist.[405]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Iceland			
Palivizumab	Palivizumab has marketing authorisation but is not marketed in Iceland. It is an 'exempt	N/A	***Implemented as part of an immunisation programme:***

	medicinal product' so may be prescribed and purchased.[406, 407]		No[408] ***Funding status:*** Not funded as of 1 July 2024.[406]
Nirsevimab	Nirsevimab has marketing authorisation but is not marketed in Iceland.[407]	N/A	***Implemented as part of an immunisation programme:*** No[408] ***Funding status:*** No information available.[406]
Maternal vaccine	The maternal vaccine was placed on the market in March 2024.[409]	N/A	***Implemented as part of an immunisation programme:*** No[410] ***Funding status:*** Not funded as of 1 July 2024.[409]
Ireland			
Palivizumab[76]	In the first year of life, palivizumab is recommended for:[76] ▪ infants born <30 wGA ▪ infants with CLD of prematurity (defined as birth <32 wGA and requiring >21% oxygen for ≥28 days after birth) ▪ certain infants with HS-CHD, 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 pulmonary abnormality or NMD that impairs their ability to clear upper airways secretions may be considered for prophylaxis ▪ children aged <1 year who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for funding, with co-pay for some patients.

	In the second year of life, palivizumab is recommended for: ▪ children with CLD (defined as those requiring supplemental oxygen for ≥28 days 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.		
Nirsevimab[11]	In October 2023, the National Immunisation Advisory Committee recommended nirsevimab for:[11] ▪ all infants during their first RSV season ○ for infants born during the RSV season, nirsevimab should be administered as soon as is feasible, preferably prior to discharge from hospital ○ for infants born outside of the RSV season, nirsevimab should be administered with two-, four-, or six-month vaccines, between August and October ▪ infants born less than two weeks after maternal vaccination ▪ high-risk infants and children who are currently eligible to receive palivizumab (nirsevimab should replace palivizumab for this group). In April 2024, these recommendations were updated for the 2024-2025 RSV season, with nirsevimab recommended for:[78] ▪ all infants born during the RSV season, ideally prior to discharge from hospital ▪ all high-risk infants (those currently eligible for palivizumab) aged ≤1 year at the start of their first RSV	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ acceptability of the intervention ▪ preliminary surveillance data for the 2023-2024 RSV season for countries with nirsevimab immunisation programmes: ○ Spain ○ Luxembourg ○ the US.	***Implemented as part of an immunisation programme:*** To be implemented on a temporary basis for the 2024-2025 RSV season as part of the Pathfinder Programme.[12] Further analysis of cost effectiveness and programmatic considerations required to determine the most appropriate immunisation strategy for future RSV seasons.[11] ***Funding status:*** Not funded as of 1 July 2024, but will be fully funded for all infants born between September 2024 and February 2025.[12]

	season, prior to the start of the RSV season ▪ all infants aged ≤6 months at the start of the RSV season, prior to the start of the RSV season ▪ all ex-preterm infants aged <2 years with CLD in their second RSV season, prior to the start of the RSV season. ▪ Infants with severe immunocompromise during the RSV season may be considered for nirsevimab in consultation with their treating specialist. ▪ Neonates with prolonged hospitalisation from birth should receive nirsevimab shortly before discharge if discharged during or shortly before the RSV season. Earlier inpatient administration may be considered if an infant is considered at risk of RSV exposure in hospital. ▪ In the event of limited supply or programme capacity, the youngest infants (born during the RSV season) and high-risk infants in their first RSV season should be prioritised. The programme should start in late-September 2024 and finish at the end of February 2025. Starting the programme on 1 September 2024 should be considered if no catch-up programme is planned. The programme end date may be adjusted based on levels of circulating RSV.		
Maternal vaccine[11]	The National Immunisation Advisory Committee recommended the maternal vaccine for:[11] ▪ all pregnant women and administered between 24 and 36 wGA.	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ NCT04032093 ○ NCT04071158 ○ MATISSE	***Implemented as part of an immunisation programme:*** Further analysis of cost and product availability needed.[11] ***Funding status:*** Not funded as of 1 July 2024.

		▪ acceptability of the intervention	
Italy			
Palivizumab	Recommended for:[411] ▪ infants born <29 wGA and aged <1 year at the start of the RSV season ▪ infants born between 29 and 35 wGA and aged <6 months at the start of the RSV season ▪ infants aged <1 year with BPD and infants aged <2 years with BPD who require medical therapy ▪ infants with HS-CHD aged <1 year at the start of the RSV season ▪ children with cystic fibrosis, Trisomy 21, congenital diaphragmatic hernia, NMDs and immunodeficiency.	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for full funding.[412]
Nirsevimab	Nirsevimab is available on prescription from hospitals or specialists only, at the individual's expense.[413]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[413]
Maternal vaccine	The maternal vaccine is available on prescription. It has not yet been evaluated for funding.[414]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[414]
Latvia			
Palivizumab	Recommended for: ▪ infants born <29 wGA ▪ infants born from 29 to <32 wGA with additional risk factors (such as, comorbidities, being in external childcare or siblings at home) ▪ children with BPD, CHD and SCID aged <2 years.	N/A	***Implemented as part of an immunisation programme:*** No information identified. ***Funding status:***

			Not funded as of 1 July 2024.[415]
Nirsevimab	Not available[416]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	Not available[416]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Liechtenstein			
Palivizumab	Recommendations in line with consensus statement for Switzerland.[417] Recommended for: ▪ infants aged <12 months at the start of the RSV season and with severe BPD. May be considered for: ▪ children with moderate BPD ▪ children with HS-CHD.	N/A	***Implemented as part of an immunisation programme:*** Not part of an immunisation programme.[418] ***Funding status:*** Funded for former preterm infants with BPD, if indicated by a specialist neonatologist, or for children with HS-CHD, if indicated by a specialist paediatric cardiologist.[419]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A

Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Lithuania			
Palivizumab	Recommended for:[213] ▪ infants born ≤28 wGA and aged ≤1 year at the start of the RSV season ▪ infants born from 28 to 30 wGA and aged ≤6 months at the start of the RSV season ▪ infants born >30 wGA if they have additional risk factors for RSV ▪ infants with BPD during the first and second years of life.	N/A	***Implemented as part of an immunisation programme:*** No information identified. ***Funding status:*** Not funded as of 1 July 2024.[420]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Luxembourg			
Palivizumab	Available for: ▪ infants born <35 wGA ▪ children aged <2 years with BPD or HS-CHD	**N/A**	***Implemented as part of an immunisation programme:*** No ***Funding status:*** Eligible for full funding.[421]
Nirsevimab	For the 2023-2024 RSV season, recommended for:[79, 422]	▪ national and international	***Implemented as part of an***

	▪ all newborns born during the RSV season (from 1 October to 1 March), preferably before leaving hospital ▪ children aged <2 years with underlying conditions that increase the risk of serious RSV infection ▪ from 2023 as part of a catch-up, non-immune children born after 1 January 2023 and administered at the start of the RSV season (from October 2023) ▪ from 2024, all infants aged <6 months, born outside of the RSV season (April to September) and administered at the start of the RSV season. For the 2024-2025 RSV season, either nirsevimab or the maternal vaccine are recommended, according to the choice of healthcare providers and parents. If choosing nirsevimab, one dose is recommended for: ▪ infants born from September 2024 to February 2025, preferably to be administered before leaving the maternity ward ▪ for infants under 6 months (that is, born between March 2024 and August 2024), to be administered as part of a seasonal campaign starting from September 2024.[82]	epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ preliminary national surveillance data for the 2023-2024 RSV season with immunisation with nirsevimab[80]	***immunisation programme:*** Yes, for the 2023-2024 RSV season.[81] No information identified for the 2024-2025 season. ***Funding status:*** Not funded as of 1 July 2024.[83, 84]
Maternal vaccine	For the 2024-2025 RSV season, either nirsevimab or the maternal vaccine are recommended, according to the choice of healthcare providers and parents. If choosing the maternal vaccine, one dose is recommended for healthy women with a healthy pregnancy, to be administered between 32 and 36 weeks.	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ MATISSE	***Implemented as part of an immunisation programme:*** No information identified. ***Funding status:*** Not funded as of 1 July 2024.[83]
Malta			
Palivizumab	Recommended for:[63] ▪ infants born <32 wGA	N/A	***Implemented as part of an***

	▪ children aged <2 years with BPD, CHD or SCID ▪ can be considered for infants born between 32 and <35 wGA.		***immunisation programme:*** No information identified. ***Funding status:*** No information identified.
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Netherlands			
Palivizumab	Recommended for children:[87] ▪ born ≤32 wGA and aged <6 months at the start of the RSV season ▪ aged <1 year with BPD ▪ aged <2 years who need oxygen therapy for the treatment of BPD ▪ aged <2 years with HS-CHD ▪ aged <1 year with severe immunodeficiency ▪ aged <1 year with severe lung pathology due to cystic fibrosis. Palivizumab is recommended (since November 2021) for children with Trisomy 21, although it is not funded for this group unless they have CHD.	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for funding.
Nirsevimab	The Vaccinations Committee of the Health Council advised that: ▪ all children born just before or during the RSV season should be offered nirsevimab as soon	▪ national and international epidemiology and burden of disease	***Implemented as part of an immunisation programme:*** Advised for inclusion in the

	as possible after birth (within 2 weeks at most) ▪ all children born after the RSV season should be offered nirsevimab before the start of their first RSV season.[121]	▪ clinical efficacy and safety trials: ○ D5290C00003 ○ HARMONIE ○ MELODY ○ MEDLEY ▪ acceptability of the intervention ▪ international practice ▪ post-implementation surveillance in other countries: ○ Spain[86] ▪ cost-effectiveness modelling	National Immunisation Programme.[121] ***Funding status:*** Not funded as of 1 July 2024. Will be funded if a decision is made to include in the National Immunisation Programme. For children in their second year of life who would be eligible for palivizumab, the decision on funding was referred to the Dutch Healthcare Institute.[121]
Maternal vaccine	The Vaccinations Committee of the Health Council advised offering nirsevimab instead of offering the maternal vaccine.[121]	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials: ○ NCT04071158 ○ MATISSE ▪ acceptability of the intervention ▪ international practice ▪ cost-effectiveness modelling	***Implemented as part of an immunisation programme:*** Not advised for inclusion in the National Immunisation Programme.[121] ***Funding status:*** Not advised for funding.[121]
Norway			
Palivizumab	Recommended for: ▪ children born <28 wGA and aged <1 year who are discharged from hospital <6 months before the start of the RSV season. ▪ children born between 28 and 31 wGA and aged <1 year with BPD (defined as requiring supplemental oxygen or respiratory support at 36 weeks postmenstrual age) and discharged from hospital <6	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for funding.

	months before start of RSV season. ▪ children born <32 wGA in their second year of life with CLD or BPD who need oxygen at home. ▪ children aged <2 years with heart disease. ▪ children aged <2 years with another serious chronic illness. ○ children aged <1 year with long-term mechanic ventilation, congenital respiratory anomalies or neuromuscular disease with reduced ability to remove respiratory secretions ○ children aged <2 years who are significantly immunocompromised during the RSV season ○ children in their second year of life with long-term mechanical ventilation with additional risk factors (such as, heart or interstitial lung disease with chronic oxygen demand).		
Nirsevimab	Not marketed in Norway as of 1 July 2024.[423] If it becomes available, the Norwegian Association of Paediatricians will recommend that nirsevimab be chosen over palivizumab for practical reasons, subject to price.[155]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	Approved and can be considered for pregnant women between 24 and 36 wGA, noting the effect appears to be best between 30 and 36 wGA.[88]	N/A	***Implemented as part of an immunisation programme:*** No ***Funding status:*** Not funded as of 1 July 2024.[423]
Poland			

Palivizumab	Recommended for:[424] ▪ infants aged <6 months and born 29 to <33 wGA or born ≤35 wGA and birth weight ≤1,500g ▪ infants aged <1 year and born ≤29 wGA ▪ children aged <2 years with BPD ▪ children aged <2 years with HS-CHD and with: ○ overt cardiac failure despite treatment, or ○ moderate-to-severe secondary pulmonary hypertension, or ○ cyanotic heart disease and arterial oxidation <90%. From 1 April 2024, also funded for the following off-label indications: ▪ children aged <1 year with cystic fibrosis ▪ children aged <2 years with SMA.[425]	N/A	***Implemented as part of an immunisation programme:*** Yes[426] ***Funding status:*** Eligible for full funding.
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Portugal			
Palivizumab	Recommended for:[427] ▪ infants born <29 wGA and aged <9 months ▪ infants born between 29 and <32 wGA and aged <3 months with mild BPD ▪ infants born between 32 and <34 wGA and aged ≤45 days with mild BPD	N/A	***Implemented as part of an immunisation programme:*** No ***Funding status:*** Not funded as of 1 July 2024.[428]

	▪ infants born between 32 and <34 wGA and aged between 46 days and <3 months with mild BPD and high risk of contagion ▪ infants aged ≤1 year with moderate-to-severe BPD ▪ children aged <2 years with HS-CHD (cyanotic or acyanotic) ▪ children aged <2 years with moderate-to-severe pulmonary hypertension ▪ children aged <2 years with CLD who required continuous treatment (oxygen therapy, bronchodilators, diuretics or corticosteroids) in the 6 months before the start of the RSV season ▪ children aged <2 years with NMD with respiratory impairment ▪ children aged <2 years with sequelae of severe congenital diaphragmatic hernia (requiring the use of prosthesis or ECMO) ▪ children aged <2 years with SCID, AIDS or severe immunodeficiency due to treatment.		
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[428]
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[428]
Romania			
Palivizumab	Available for infants born <35 wGA and for infants born with certain	N/A	***Implemented as part of an***

	health conditions that increase risk of severe RSV disease.[429]		***immunisation programme:*** N/A ***Funding status:*** Eligible for funding.
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Slovakia			
Palivizumab	May be indicated for:[63] ▪ children born at ≤28 wGA who are aged <6 months at the start of the RSV season ▪ children born at 29-32 wGA who are aged <6 months at the start of the RSV season ▪ children born at 33-35 wGA who are aged <3 months at the start of the RSV season and have ≥1 risk factors* ▪ children born at 33-35 wGA who are aged <6 months at the start of the RSV season and have ≥2 risk factors* *Risk factors: positive family history of wheezing, breastfeeding for less than 2 months, birth weight below 10th percentile for gestational age or less than 1500g, NMD, discharge during RSV season, history of severe respiratory difficulties in the neonatal period, cystic fibrosis, residence of a child in a collective facility, living in a household with	N/A	***Implemented as part of an immunisation programme:*** No information identified. ***Funding status:*** Funding is subject to the prior approval of the health insurance company.[430]

	more than seven people, multiple pregnancy.		
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Maternal vaccine	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Slovenia			
Palivizumab	For 2023-24, recommended for:[431] ▪ children born at <29 wGA and aged <12 months at the start of the RSV season ▪ children born at 29 to 31+6 wGA and aged <6 months at the start of the RSV season ▪ children aged <12 months with CLD (BPD) who have required oxygen therapy in the 6 months prior to the start of the RSV season ▪ children aged <2 years with HS-CHD, until the operative correction of the defect. Palivizumab is prescribed by a specialist paediatrician or, for children with cardiac impairment, by a specialist paediatric cardiologist.	N/A	***Implemented as part of an immunisation programme:*** No information identified. ***Funding status:*** Eligible for full funding through compulsory health insurance.[432]
Nirsevimab	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A

Maternal vaccine	A recommendation for vaccination of pregnant women against RSV is under consideration, having been proposed in a meeting of the Slovenian NITAG in February 2024.[433]	N/A	***Implemented as part of an immunisation programme:*** Proposed for inclusion in the immunisation schedule for 2024.[433] ***Funding status:*** N/A
Spain			
Palivizumab	Recommended and funded for:[142] ▪ children born ≤35 wGA and aged <6 months at the start of the RSV season ▪ children aged <2 years and required treatment for BPD in previous six months ▪ children aged <2 years with HS-CHD.	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for full funding.
Nirsevimab	A temporary recommendation was in place for nirsevimab for the 2023-2024 RSV season, in order of priority:[142] ▪ paediatric population at high risk of severe disease from RSV ○ infants born <35 wGA and aged <1 year at the start of the RSV season ○ infants aged <2 years with HS-CHD or BPD ○ infants aged <2 years with other underlying risk factors for severe disease including immunosuppression, inborn errors of metabolism, neuromuscular diseases, severe lung diseases, genetic syndromes with respiratory problems, Trisomy 21, cystic fibrosis and those in palliative care. ▪ any infant born during the RSV season (from 25 September 2023 to 31 March 2024)	▪ national and international epidemiology and burden of disease ▪ clinical efficacy and safety trials ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ organisational considerations ▪ review of economic evaluations ▪ ethical considerations[142] ▪ effectiveness, impact, safety and acceptability of nirsevimab in the 2023-2024 season (data available up to February 2024)[90]	***Implemented as part of an immunisation programme:*** Yes, although each autonomous region of Spain is responsible for the approach to, and timing of, implementation of the national recommendations.[86, 142] ***Funding status:*** Eligible for full funding.[96]

	▪ infants aged <6 months at start of RSV season (that is, infants born from 1 April 2023 to March 31 2024). For the 2024-2025 season, nirsevimab is recommended for:[90] ▪ paediatric population at high risk of severe disease from RSV – recommended for the same groups in the same order of priority as in the 2023-2024 season ○ infants born <35 wGA who received a dose of nirsevimab in the 2023-2024 season may receive another dose at the start of the 2024-2025 season if they are aged <1 year ○ children with HS-CHD, BPD, or other underlying risk factors for severe disease who received a dose of nirsevimab in the 2023-2024 season may receive another dose if they are aged <2 years at the time of administration. ▪ infants born between 1 April 2024 and 31 March 2025 ▪ infants born from October 2024 to March 2025 should preferably receive nirsevimab in the first 24-48 hours after birth, or as soon as possible. Recommendations for subsequent seasons will be reviewed and updated to include other preventive strategies, such as maternal vaccines.[90, 142]		
Maternal vaccine	Recommendations for subsequent seasons will be reviewed and updated to include other preventive strategies, such as maternal vaccines.[90, 142] The maternal vaccine is marketed and available on prescription.[434]	N/A	***Implemented as part of an immunisation programme:*** No ***Funding status:*** Eligible for full funding[95]

Sweden			
Palivizumab	A temporary recommendation is in place for the 2023-2024 RSV season that palivizumab is recommended, if nirsevimab is unavailable, for:[97] ▪ infants aged <1 year of age and born <26 wGA ▪ infants aged <1 year of age with severe heart and lung diseases, including BPD ▪ children aged <2 years who received palivizumab during the 2022-2023 RSV season according to the 2015 treatment recommendations[435] ○ children with severe BPD who require oxygen therapy ○ children with complicated heart failure, such as univentricular heart or other palliated heart defects.	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for full funding.[436, 437]
Nirsevimab	For the 2023-2024 RSV season, a temporary recommendation was in place for infants aged <1 year during their first RSV season, in order of priority according to the following risk groups:[97] ▪ risk group 1: nirsevimab (or palivizumab if nirsevimab is unavailable), for those born <26 wGA and those with severe heart and lung diseases, including BPD (priority group for 2023-2024) ▪ risk group 2: nirsevimab, if available, for those born <32 wGA, those with chronic heart disease or heart failure, CLD with respiratory support therapy, congenital paediatric surgical conditions, neurological conditions and those who are immunocompromised (priority group for 2023-2024) ▪ risk group 3: nirsevimab, if available, to infants aged <3 months (provided equitable	Expert group consensus based on the approved product information and 2015 recommendation on the management of RSV infections and considered: ▪ national epidemiology and burden of disease ▪ clinical efficacy and safety trials ○ D5290C00003 ○ HARMONIE ○ MEDLEY ○ MELODY ▪ observational study of clinical effectiveness in the 2023-2024 season: ○ NIRSE-GAL	***Implemented as part of an immunisation programme:*** Not available as of 1 July 2024.[438] ***Funding status:*** N/A

	national implementation can take place for this group). ▪ risk group 4: nirsevimab, if available, to infants aged <1 year (provided an equal national implementation can take place for this group). Use of nirsevimab for children older than 12 months is currently off-label and an application is currently under consideration by the EMA. In May 2024, the Swedish Medical Products Agency recommended immunisation with monoclonal antibodies for infants aged 0-12 months, with nirsevimab recommended over palivizumab. If nirsevimab availability is limited, infants at high risk should be prioritised according to the risk groups listed above.(98) In the context of maternal vaccination, the following recommendations can be applied to infants aged <3 months or to infants aged <12 months, based on national or regional priority decisions. Nirsevimab is recommended for all infants in their first RSV season if the mother is not adequately vaccinated. If the mother has been vaccinated >14 days before birth, nirsevimab is recommended for infants: ▪ born <32 wGA ▪ infants at high risk of severe RSV disease born ≥32 wGA. Nirsevimab is not recommended for infants without risk factors born ≥32 wGA, if the mother was vaccinated >14 days before birth.(98)		
Maternal vaccine	National recommendations on vaccination, including the maternal vaccine, are referred to the Swedish Public Health Agency. Recommendations regarding the maternal vaccine were therefore not included in the temporary recommendation for the 2023-2024 RSV season or the May 2024	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/I

	recommendation from the Swedish Medical Products Agency.		
United Kingdom			
Palivizumab	Recommended for children in high risk groups:[439] ▪ high risk due to BPD ○ preterm infants who have moderate or severe BPD ○ infants with respiratory diseases who are not necessarily preterm but who remain on oxygen at the start of the RSV season ▪ high risk due to CHD ○ preterm infants with acyanotic HS-CHD at start of RSV season as follows: aged <9 months and born ≤24 wGA; aged <6 months and born <28 wGA; aged <3 months and born <32 wGA; aged <1.5 months and born <34 wGA. ○ infants with cyanotic or acyanotic CHD plus significant co-morbidities ▪ high risk due to SCID ○ children aged <24 months with SCID.	N/A	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for funding.
Nirsevimab	In February 2023, the JCVI advised that palivizumab should be replaced with nirsevimab for the children currently eligible to receive palivizumab.[102] In September 2023, the JCVI advised that antibody prophylaxis should be considered in a universal programme for the immunisation of infants against RSV. The advice is under consideration by the government.[102, 440] In June 2024, the UK Health Security Agency outlined the RSV immunisation programme for the	▪ national and international epidemiology and burden of disease ▪ clinical studies to assess burden of RSV ○ STOP RSV ○ BronchStart ▪ clinical efficacy and safety trials ○ HARMONIE ○ MELODY ▪ cost-effectiveness modelling	***Implemented as part of an immunisation programme:*** No ***Funding status:*** N/A

	2024-2025 season; nirsevimab was not included in this publication.[103]		
Maternal vaccine	In September 2023, the JCVI advised that maternal immunisation should be considered in a universal programme for the immunisation of infants against RSV. The advice is under consideration by the government.[102, 440] In June 2024, the UK Health Security Agency outlined that from 1 September 2024, women who are at least 28 weeks pregnant should be offered a single dose of the RSV vaccine (RSVpreF – Abrysvo®), ideally at the 28-week antenatal visit. Pregnant women remain eligible for vaccination up to birth.[103]	▪ national and international epidemiology and burden of disease ▪ clinical studies to assess burden of RSV ○ STOP RSV ○ BronchStart ▪ clinical efficacy and safety trials ○ MATISSE ▪ cost-effectiveness modelling	***Implemented as part of an immunisation programme:*** Yes ***Funding status:*** Eligible for funding

Key: AIDS – acquired immunodeficiency syndrome; BPD – bronchopulmonary dysplasia; CHD – congenital heart disease; CLD – chronic lung disease; CPAP – continuous positive airway pressure; ECMO – extracorporeal membrane oxygenation; HS-CHD – haemodynamically significant congenital heart disease; JCVI – Joint Committee on Vaccination and Immunisation; N/A – not applicable; N/I – no information identified; NICU – neonatal intensive care unit; NMD – neuromuscular disease; RSV – respiratory syncytial virus; SCID – severe combined immunodeficiency; STIKO – Standing Committee on Vaccination; wGA – weeks gestational age.

Table 2 Summary of recommendations for the prevention of RSV in older adults, as of 1 July 2024

Country	Recommendation	Evidence underpinning recommendation	Implemented as part of an immunisation programme Funding status
Austria			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	Recommended for adults aged ≥60 years. Vaccination may be considered for off-label use for adults aged ≥18 years with certain risk factors: ▪ severe decompensated organ diseases ▪ people with cancer ▪ people with immunodeficiency, severe respiratory, cardiac, renal, endocrine, metabolic or neurological diseases ▪ people with class 1 obesity ▪ people with HIV or other immunosuppressive diseases ▪ people cared for in retirement or nursing homes. No preference specified between the two RSV vaccines authorised at the time of the recommendation.(64)	No information identified.	***Implemented as part of an immunisation programme:*** Recommended and available, at a cost to the individual, as part of the Austrian vaccination plan 2023-2024.(64) ***Funding status:*** Not funded as of 1 July 2024.
Belgium			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	RSV vaccination can be offered on an individual basis to high risk patients aged ≥60 years with at least one risk factor of severe RSV disease. Risk factors for severe RSV disease include: ▪ chronic respiratory diseases (COPD, asthma, bronchiectasis, interstitial lung diseases, chronic respiratory failure)	▪ international and national epidemiology and burden of disease estimates ▪ clinical efficacy and safety data	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme. ***Funding status:*** Not funded as of 1 July 2024.(136)

	▪ chronic heart failure ▪ chronic kidney disease ▪ diabetes ▪ obesity ▪ immunodeficiency, including patients with solid cancer or haematologic malignancy, use of immunosuppressive medications, solid organ transplantation and allogeneic HSCT ▪ institutionalised patients.[135]		
Bulgaria			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[380]
Croatia			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Cyprus			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** No.[441] ***Funding status:*** N/A
Czech Republic			
RSV vaccine (RSVpreF (Abrysvo®) or	No information identified for national recommendation. Available, on an individual basis, for adults aged ≥60 years at certain hospitals.[137]	N/A	***Implemented as part of an immunisation programme:***

RSVPreF3 (Arexvy®))			Available but not part of an immunisation programme. ***Funding status:*** Not eligible for full funding as of 1 July 2024.[161, 386] Individual insurance companies provide partial funding.[137, 138]
Denmark			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	RSV vaccines are available for adults aged ≥60 years, but there is no national recommendation regarding vaccination of adults against RSV in Denmark.[391]	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme.[391] ***Funding status:*** Not funded as of 1 July 2024.[391]
Estonia			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified. RSV is not listed on diseases and vaccines page of the Estonian Health Fund Vaccinate website.[442]	N/A	***Implemented as part of an immunisation programme:*** No.[394] ***Funding status:*** N/A
Finland			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	RSV vaccines are available to buy, with a doctor's prescription, from private healthcare and pharmacies for adults aged ≥60 years.[397]	N/A	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme. ***Funding status:*** Not funded as of 1 July 2024.[396]
France			

RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	An assessment of the vaccination of older adults against RSV is ongoing by the Haute Autorité de Santé. This will include all adults aged ≥65 years regardless of risk, and adults aged between 60 and 64 years at high risk of serious complications resulting from RSV infection. A decision is expected in July 2024.[139]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Germany			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	In 2023, a collaborative position paper was published by German medical societies and organisations recommending vaccination of adults aged ≥60 years.[443] The German Standing Committee on Vaccination (STIKO) is currently evaluating RSV prevention options, and is expected to publish its comments by summer 2024.[140] Both vaccines are available from pharmacies.	N/A	***Implemented as part of an immunisation programme:*** No. ***Funding status:*** Not funded as of 1 July 2024. Costs may be covered by health insurance on an individual basis.[140, 443]
Greece			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information on RSV vaccines included in December 2023 recommendations on protection against respiratory infections issued by the Ministry of Health and Public Health Emergency Response Committee.[444]	N/A	***Implemented as part of an immunisation programme:*** No.[445] ***Funding status:*** N/A
Hungary			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Iceland			

RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No recommendations identified.[410] Abrysvo® placed on the market in March 2024.[409] No information on Arexvy® identified.	N/A	***Implemented as part of an immunisation programme:*** No.[410] ***Funding status:*** Not funded as of 1 July 2024.[409]
Ireland			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	In October 2023, the National Immunisation Advisory Committee recommended vaccination against RSV for adults aged ≥65 years with either RSV vaccine.[11]	▪ national epidemiology and burden of disease estimates ▪ clinical efficacy and safety data ▪ acceptability considerations	***Implemented as part of an immunisation programme:*** No. Further analysis of cost and product availability is needed. ***Funding status:*** Not funded as of 1 July 2024.
Italy			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No national recommendation noted for vaccination of older adults against RSV. RSVPreF3 (Arexvy®) is available on prescription and must be paid for by the individual. RSVpreF (Abrysvo®) is available on prescription but has not yet been evaluated for funding.[414, 446]	N/A	***Implemented as part of an immunisation programme:*** No.[447] ***Funding status:*** Not funded as of 1 July 2024.[414, 446]
Latvia			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** No.[448] ***Funding status:*** N/A
Liechtenstein			
RSV vaccine (RSVpreF (Abrysvo®) or	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A

RSVPreF3 (Arexvy®))			***Funding status:*** N/A
Lithuania			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No national recommendation noted for vaccination of older adults against RSV.[420, 449]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Luxembourg			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No national recommendation noted for vaccination of older adults against RSV.[450]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[421]
Malta			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Netherlands			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No national recommendation noted for vaccination of older adults against RSV.[121, 451] RSV vaccines are available on prescription, but are not funded and must be paid for privately by the individual.[452]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[453, 454]
Norway			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	The RSV vaccine can be considered for adults aged 60 years and older with an underlying disease.[88]	Advice based on summary of product characteristics.[88]	***Implemented as part of an immunisation programme:*** Available but not part of an

			immunisation programme. ***Funding status:*** Not funded as of 1 July 2024.[88, 423]
Poland			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Portugal			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified for national recommendation. RSV vaccines are available on prescription, but are not funded and must be paid for privately by the individual.[428]	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** Not funded as of 1 July 2024.[428]
Romania			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** N/A ***Funding status:*** N/A
Slovakia			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No information identified.	N/A	***Implemented as part of an immunisation programme:*** No.[455] ***Funding status:*** N/A
Slovenia			
RSV vaccine (RSVpreF (Abrysvo®) or	No information identified.	N/A	***Implemented as part of an***

RSVPreF3 (Arexvy®))			***immunisation programme:*** N/A ***Funding status:*** N/A
Spain			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	No recommendation identified. The Public Health Commission has stated that recommendations and target groups for RSV prevention strategies will be reviewed for upcoming RSV seasons.[90, 142] RSV vaccines are marketed and available on prescription.[434]	N/A	***Implemented as part of an immunisation programme:*** No ***Funding status:*** N/I
Sweden			
RSV vaccine (RSVpreF (Abrysvo®) or RSVPreF3 (Arexvy®))	For the 2023/2024 RSV season, recommended for:[143] ▪ adults aged ≥75 years ▪ adults aged ≥60 with the following risk factors – ○ chronic lung disease (such as COPD or unstable asthma) ○ chronic cardiovascular disease, including stroke and excluding hypertension ○ conditions that lead to reduced lung function, impaired cough force or secretion stagnation (such as class 3 obesity, neuromuscular diseases, or multifunction impairment) ○ chronic liver or kidney failure ○ type 1 or 2 diabetes mellitus ○ immunocompromising conditions or treatments ○ adults with frailty who require help with daily life activities. Recommendations may change for the 2024/2025 season.	▪ national epidemiology and burden of disease estimates ▪ clinical efficacy and safety data	***Implemented as part of an immunisation programme:*** Available but not part of an immunisation programme. ***Funding status:*** N/I[100]

United Kingdom			
RSV vaccine (RSVpreF (Abrysvo®)	In September 2023, the Joint Committee on Vaccination and Immunisation advised that a programme of one-off RSV vaccination be implemented for adults aged ≥75 years. The committee suggested an initial programme to vaccinate adults aged from 75 to 80 years, and then for those turning 75 in subsequent years.[102] In June 2024, the UK Health Security Agency outlined that from 1 September 2024, all adults turning 75 years on or after that date will be eligible for a single dose of RSV vaccine (RSVpreF – Abrysvo®) as part of the routine RSV vaccination programme. A one-off catch-up campaign will run between 1 September 2024 and 31 August 2025, for people aged 75 to 79 years. Individuals will remain eligible until the day before their 80th birthday, with the exception of people who turn 80 in the first year who have until 31 August 2025 to get vaccinated.[103]	▪ national epidemiology and burden of disease estimates ▪ clinical efficacy and safety data ▪ cost-effectiveness modelling	***Implemented as part of an immunisation programme:*** Yes. ***Funding status:*** Eligible for funding.

Key: COPD – chronic obstructive pulmonary disease; HSCT – haematopoietic stem cell transplantation; N/A – not applicable; N/I – no information identified; NITAG – National Immunisation Technical Advisory Group; RSV – respiratory syncytial virus.

Appendix 5.A

Table 1 Immunisation of infants aged less than one year and eligible for palivizumab – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	240	N/A	N/A
Immunoprophylaxis uptake (%)	100	N/A	N/A
Clinical efficacy of immunisation – nirsevimab	56%*	37%*	71%*
Clinical effectiveness of immunisation – palivizumab	56%	37%	71%
RSV incidence (rate per 100,000)	4,290	3,648	4,979
Likelihood of hospital discharge (any) if RSV positive	83%	71%	93%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	9%	7%	11%
Likelihood of death if RSV positive	0%	0%	0.01%
Hospital length of stay (days)	4.3	3.4	5.2
Hospital length of stay that included an ICU stay (days)	10.9	7.5	14.8
Cost of hospital episode (any)	€9,739	€8,615	€10,931
Cost of hospital episode day (which included an ICU stay)	€31,453	€19,149	€46,760

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.
*Given the absence of evidence of efficacy of nirsevimab specifically in infants at high risk of severe disease from RSV, an assumption was made that its efficacy was the same as that of palivizumab in this population.

Table 2 Immunisation of infants aged less than two years and eligible for palivizumab – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	581	N/A	N/A
Immunoprophylaxis uptake (%)	100	N/A	N/A
Clinical efficacy of immunisation – nirsevimab	56%*	37%*	71%*
Clinical effectiveness of immunisation – palivizumab	56%	37%	71%
RSV incidence (rate per 100,000)	2,891	2,788	2,996
Likelihood of hospital discharge (any) if RSV positive	78%	76%	79%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	9%	7%	10%
Likelihood of death if RSV positive	0.03%	0%	0.18%
Hospital length of stay (days)	4.2	2.2	6.8
Hospital length of stay that included an ICU stay (days)	10.8	7.4	14.8
Cost of hospital episode (any)	€9,739	€8,615	€10,931
Cost of hospital episode day (which included an ICU stay)	€31,453	€19,149	€46,760

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.
*Given the absence of evidence of efficacy of nirsevimab specifically in infants at high risk of severe disease from RSV, an assumption was made that its efficacy was the same as that of palivizumab in this population.

Table 3 Seasonal infant strategy – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	27,807	N/A	N/A
Immunoprophylaxis uptake (%)	88.1%	80.5%	95.6%
Clinical efficacy of immunisation	80%	70%	87%
RSV incidence (rate per 100,000)	4,290	3,648	4,979
Likelihood of hospital discharge (any) if RSV positive	83%	71%	93%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	9%	7%	11%
Likelihood of death if hospitalised	0%	0%	0.01%
Hospital length of stay (days)	4.3	3.4	5.2
Hospital length of stay that included an ICU stay (days)	10.9	7.5	14.8
Cost of hospital episode (any)	€9,739	€8,615	€10,931
Cost of hospital episode day (which included an ICU stay)	€31,453	€19,149	€46,760

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

Table 4 Seasonal and catch-up infant strategy – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	55,678	N/A	N/A
Immunoprophylaxis uptake (%)	88.1%	80.5%	95.6%
Clinical efficacy of immunisation	80%	70%	87%
RSV incidence (rate per 100,000)	4,290	3,648	4,979
Likelihood of hospital discharge (any) if RSV positive	83%	71%	93%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	9%	7%	11%
Likelihood of death if hospitalised	0%	0%	0.01%
Hospital length of stay (days)	4.3	3.4	5.2
Hospital length of stay that included an ICU stay (days)	10.9	7.5	14.8
Cost of hospital episode (any)	€9,739	€8,615	€10,931
Cost of hospital episode day (which included an ICU stay)	€31,453	€19,149	€46,760

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

Table 5 Hybrid infant strategy – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	33,140	N/A	N/A
Immunoprophylaxis uptake (%)	88.1%	80.5%	95.6%
Clinical efficacy of immunisation	80%	70%	87%
RSV incidence (rate per 100,000)	4,290	3,648	4,979
Likelihood of hospital discharge (any) if RSV positive	83%	71%	93%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	9%	7%	11%
Likelihood of death if hospitalised	0%	0%	0.01%
Hospital length of stay (days)	4.3	3.4	5.2
Hospital length of stay that included an ICU stay (days)	10.9	7.5	14.8
Cost of hospital episode (any)	€9,739	€8,615	€10,931
Cost of hospital episode day (which included an ICU stay)	€31,453	€19,149	€46,760

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

Table 6 Maternal immunisation strategy – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Maternal Population	27,433	N/A	N/A
Eligible Infant Population	27,927	N/A	N/A
Immunoprophylaxis uptake (%)	62.0%	54.5%	69.5%
Clinical efficacy of immunisation	70.9%	46%	86%
RSV incidence (rate per 100,000)	4,290	3,648	4,979
Likelihood of hospital discharge (any) if RSV positive (unvaccinated)	83%	71%	93%
Likelihood of hospital discharge (any) if RSV positive (vaccinated)	100%	N/A	N/A
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	9%	7%	11%
Likelihood of death if RSV positive	0%	0%	0.01%
Hospital length of stay (days)	4.3	3.5	5.2
Hospital length of stay that included an ICU stay (days)	10.9	8.0	15.5
Cost of hospital episode (any)	€9,739	€8,615	€10,931
Cost of hospital episode day (which included an ICU stay)	€31,453	€19,149	€46,760

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

Table 7 Immunisation of adults aged 65 years and older with RSVpreF – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	840,830	N/A	N/A
Immunoprophylaxis uptake (%)	75.6%	68.1%	83.1%
Clinical efficacy of immunisation	88.9%	58.9%	98.6%
RSV incidence (rate per 100,000)	189	163	217
Likelihood of hospital discharge (any) if RSV positive	9%	8.5%	12%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	7%	7.3%	7.6%
Likelihood of death if RSV positive	0.6%	0.2%	1.1%
Hospital length of stay (days)	10.0	7.7	12.5
Hospital length of stay that includes an ICU stay (days)	17.9	13.9	22.5
Cost of hospital episode (w/o ICU)	€11,002	€8,041	€14,420
Cost of hospital episode day (w/ICU)	€40,982	€29,951	€53,715

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

Table 8 Immunisation of adults aged 65 years and older with RSVPreF3 – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	840,830	N/A	N/A
Immunoprophylaxis uptake (%)	75.6%	68.1%	83.1%
Clinical efficacy of immunisation	82.6%	59.2%	94.2%
RSV incidence (rate per 100,000)	189	163	217
Likelihood of hospital discharge (any) if RSV positive	9%	8.5%	12%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	7%	7.3%	7.6%
Likelihood of death if RSV positive	0.6%	0.2%	1.1%
Hospital length of stay (days)	10.0	7.7	12.5
Hospital length of stay that includes an ICU stay (days)	17.9	13.9	22.5
Cost of hospital episode (w/o ICU)	€11,002	€8,041	€14,420
Cost of hospital episode day (w/ICU)	€40,982	€29,951	€53,715

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

Table 9 Immunisation of adults aged 75 years and older with RSVpreF – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	381,856	N/A	N/A
Immunoprophylaxis uptake (%)	87.1%	76.9%	94.6%
Clinical efficacy of immunisation	88.9%	58.9%	98.6%
RSV incidence (rate per 100,000)	290	258	325
Likelihood of hospital discharge (any) if RSV positive	9.3%	8.3%	12.3%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	6.9%	2.9%	13.9%
Likelihood of death if RSV positive	0.6%	0.2%	1.1%
Hospital length of stay (days)	11.2	7.4	15.8
Hospital length of stay that includes an ICU stay (days)	17.9	13.9	22.5
Cost of hospital episode (w/o ICU)	€11,002	€8,041	€14,420
Cost of hospital episode day (w/ICU)	€40,982	€29,951	€53,715

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

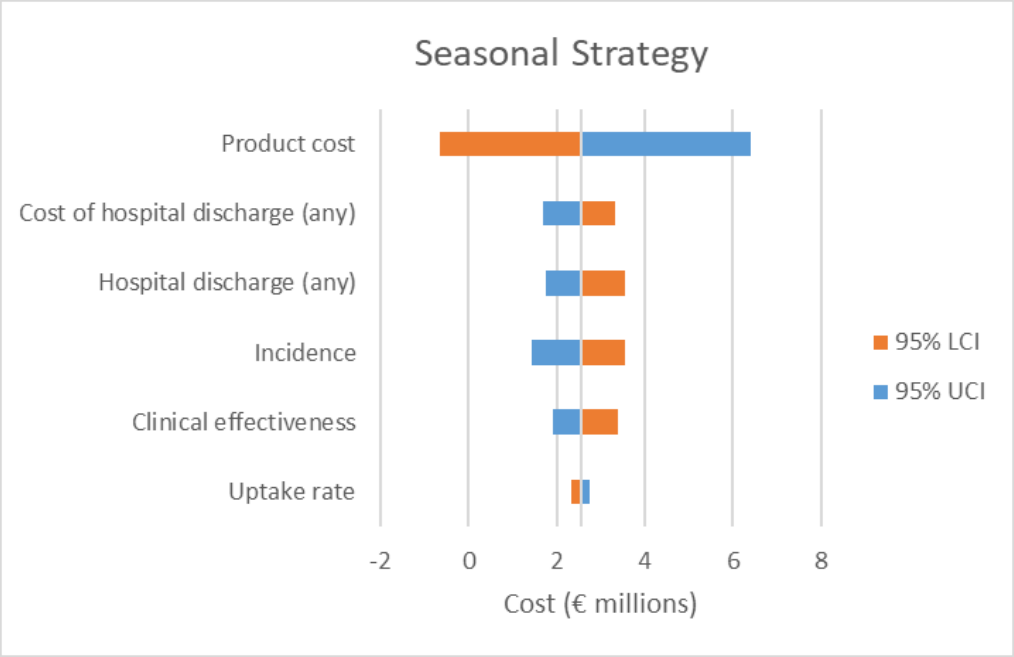
Table 10 Immunisation of adults aged 75 years and older with RSVPreF3 – parameter values used in the sensitivity analysis

Parameter	Mean (Deterministic Value)	95% LCI	95% UCI
Eligible Population	381,856	N/A	N/A
Immunoprophylaxis uptake (%)	87.1%	76.9%	94.6%
Clinical efficacy of immunisation	82.6%	59.2%	94.2%
RSV incidence (rate per 100,000)	290	258	325
Likelihood of hospital discharge (any) if RSV positive	9.3%	8.3%	12.3%
Likelihood of hospital discharge (which included an ICU stay) if RSV positive	6.9%	2.9%	13.9%
Likelihood of death if RSV positive	0.6%	0.2%	1.1%
Hospital length of stay (days)	11.2	7.4	15.8
Hospital length of stay that includes an ICU stay (days)	17.9	13.9	22.5
Cost of hospital episode (w/o ICU)	€11,002	€8,041	€14,420
Cost of hospital episode day (w/ICU)	€40,982	€29,951	€53,715

Key: ICU – intensive care unit; LCI – lower confidence interval; N/A – not applicable; RSV – respiratory syncytial virus; UCI – upper confidence interval.

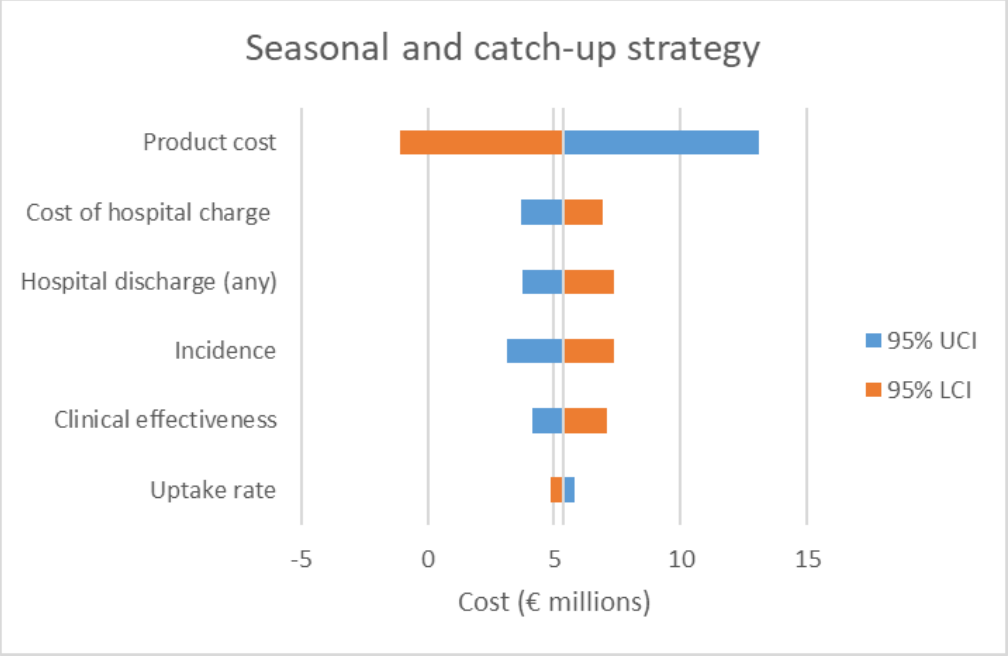
Appendix 5.B

Figure 1 Tornado plot of one-way sensitivity analysis of the incremental costs for the seasonal infant immunisation strategy



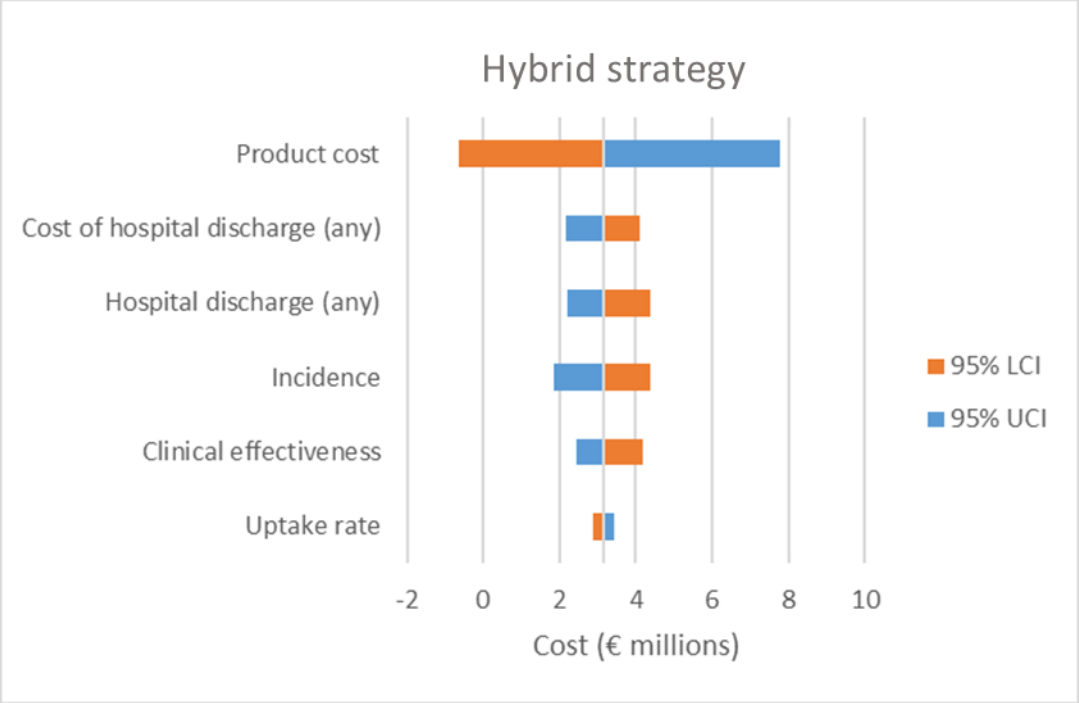
Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 2 Tornado plot of one-way sensitivity analysis of the incremental costs for the seasonal and catch-up infant immunisation strategy



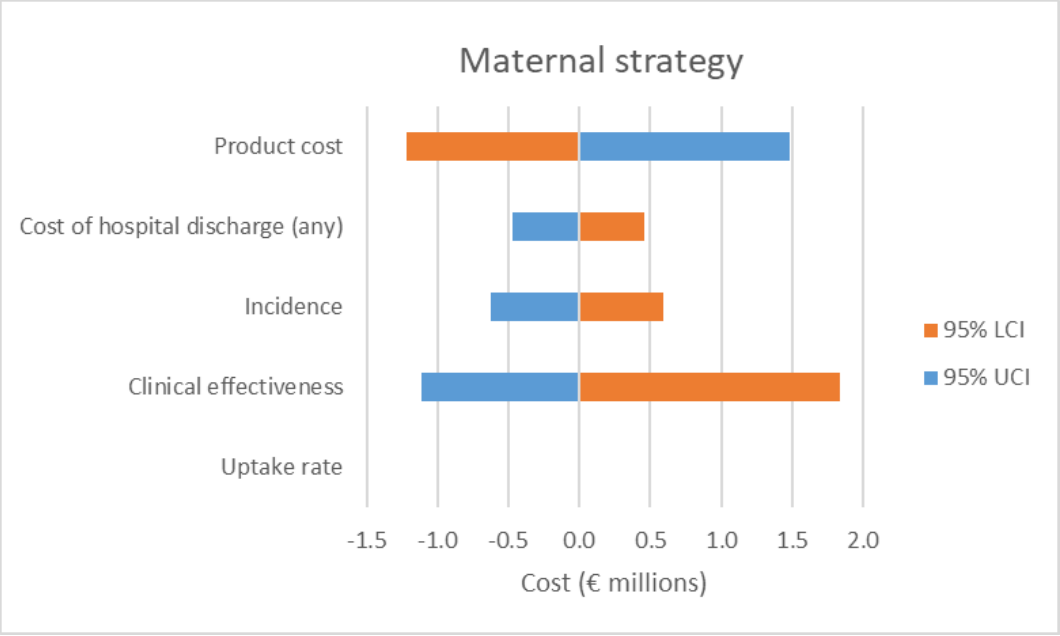
Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 3 Tornado plot of one-way sensitivity analysis of the incremental costs for the hybrid immunisation strategy for infants



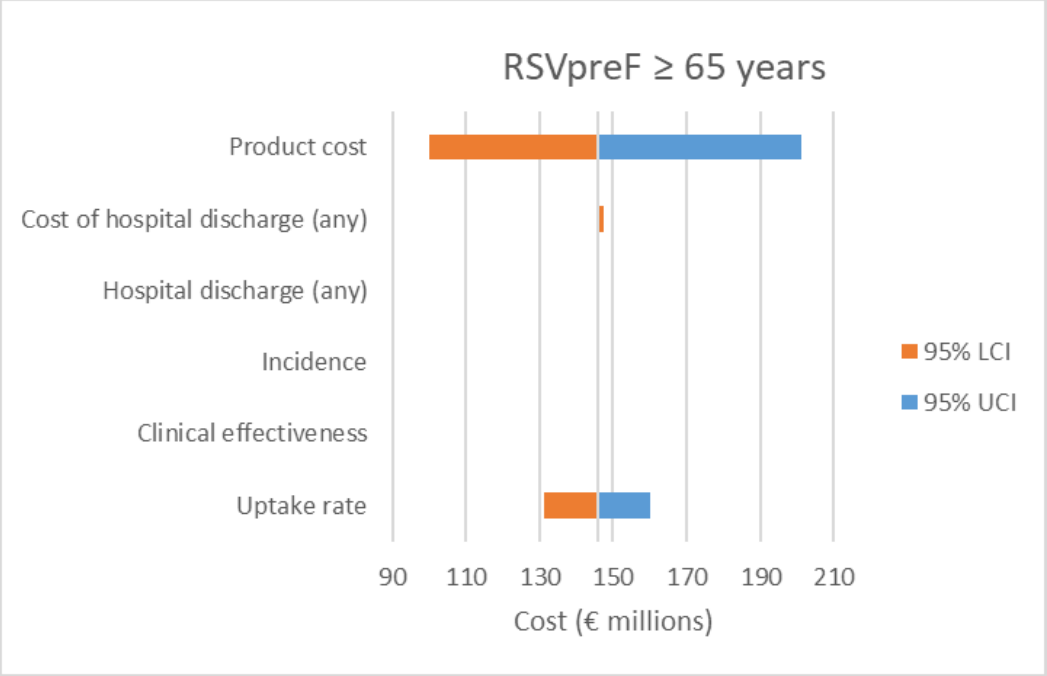
Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 4 Tornado plot of one-way sensitivity analysis of the incremental costs for the maternal immunisation strategy



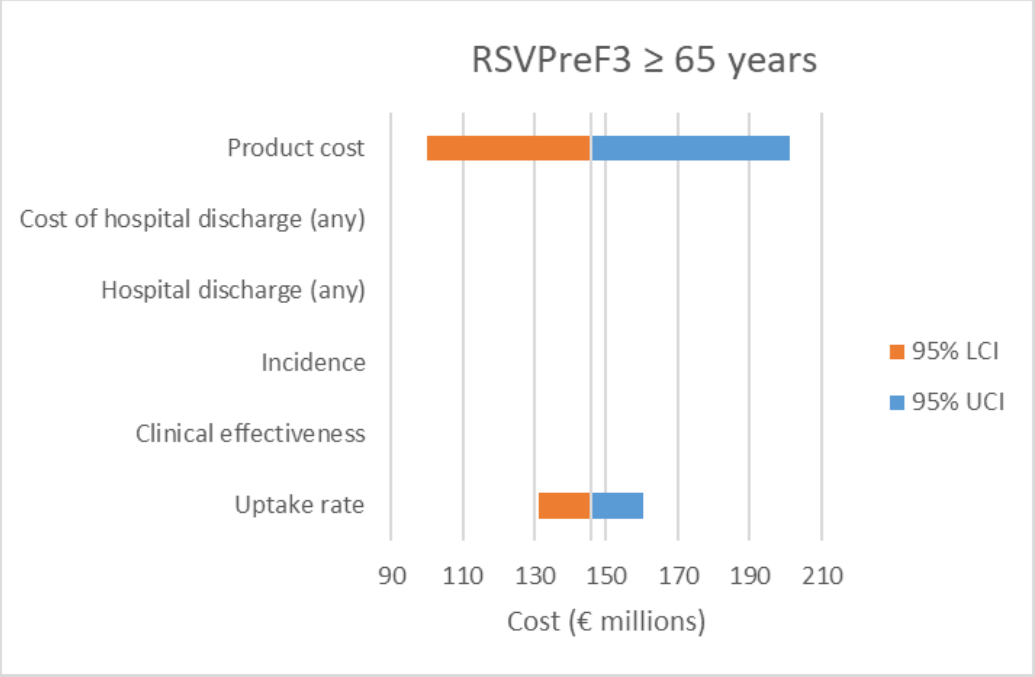
Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 5 Tornado plot of one-way sensitivity analysis of the incremental costs of immunisation of adults aged 65 years and older with RSVpreF



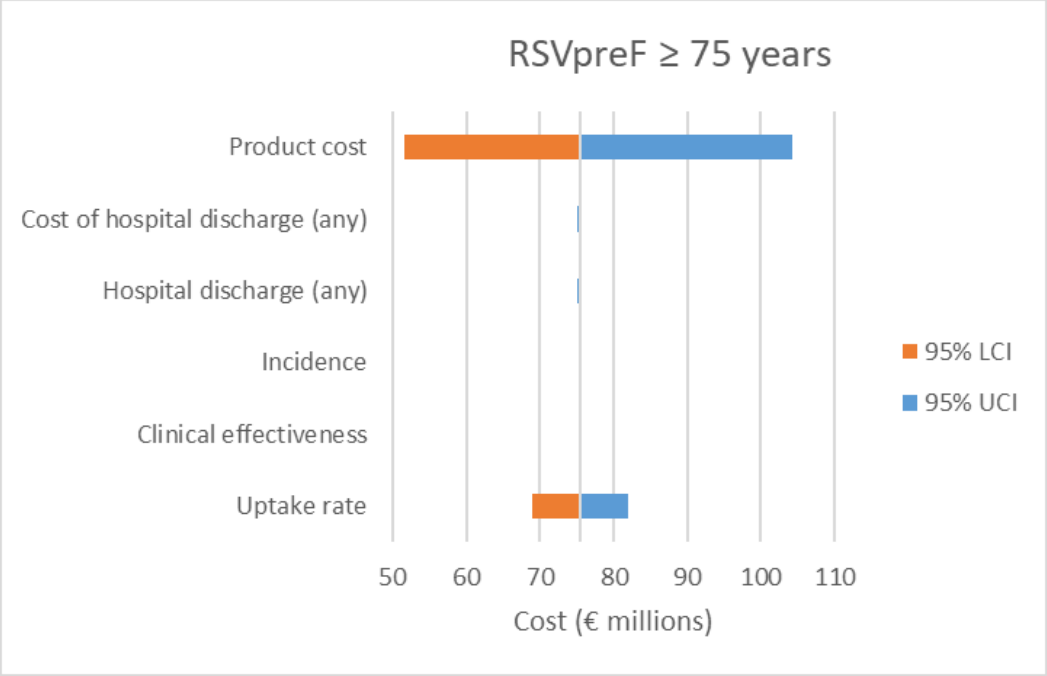
Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 6 Tornado plot of one-way sensitivity analysis of the incremental costs of immunisation of adults aged 65 years and older with RSVPreF3



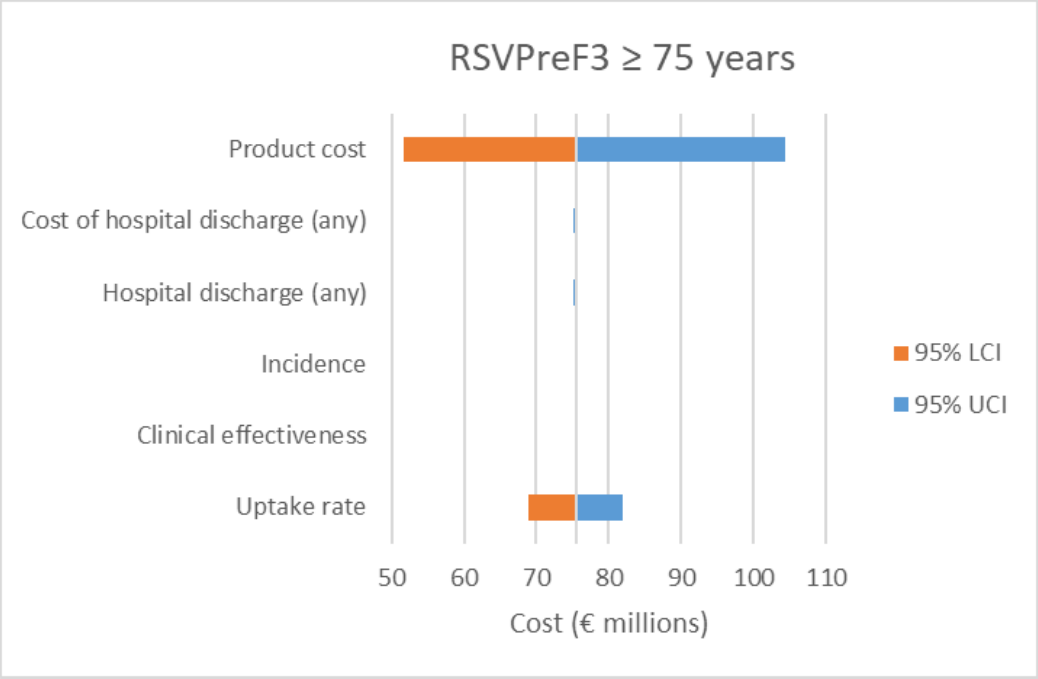
Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 7 Tornado plot of one-way sensitivity analysis of the incremental costs of immunisation of adults aged 75 years and older with RSVpreF



Key: LCI – lower confidence interval; UCI – upper confidence interval.

Figure 8 Tornado plot of one-way sensitivity analysis of the incremental costs of immunisation of adults aged 75 years and older with RSVPreF3



Key: LCI – lower confidence interval; UCI – upper confidence interval.

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