Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for a rapid health technology assessment of immunisation against respiratory syncytial virus in Ireland

13 August 2024

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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.

1. Introduction

1.1. Background

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 ribonucleic acid (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] A systematic review of the global distribution of RSV A and B infections, published in 2022, found that RSV A has been 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 children are infected with RSV by the time they are two years old. Reinfection with RSV throughout a person's lifetime is common, but disease severity tends to be reduced with repeated exposure.[5] Infants aged six months and under are at higher risk of hospitalisation and serious outcomes due to RSV.[2] Most RSV infections in children are mild and lead to 'flu-like' symptoms often accompanied by otitis media (middle ear infection). However, in some children, RSV infections may result in bronchiolitis, pneumonia and croup.[5] Furthermore, RSV infection in early life has been associated with the development of recurrent wheeze of early childhood or asthma later in life, though causality has not yet been established.[6] 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 contributing to significant morbidity and mortality in this population.[5]

Globally, in 2019, it was estimated that in children aged five years of age and younger, there were 33 million RSV-associated ALRI episodes, 3.6 million RSV-associated ALRI hospital admissions, 26,300 RSV-associated ALRI in-hospital deaths, and 101,400 RSV-attributable overall deaths.[7] In those aged six months and younger, RSV infection accounted for approximately half of the total hospitalised ALRI cases in high-income countries during the same time period.[7] Considering the population aged 60 years and older, again in 2019, there were 5.2 million RSV-associated ALRI episodes, 470,000 RSV-associated ALRI hospital admissions, and 33,000 RSV-associated ALRI in-hospital deaths reported in high-income countries.[8] However, there are fewer viruses present in the respiratory secretions of older adults compared with children. As such, older adults are often not investigated

microbiologically, which results in an underestimation of RSV infections in this population group.[9]

In Ireland, RSV outbreaks typically occur in the winter months, with the highest numbers of infections usually reported in December and January — although RSV activity can peak earlier. For example, during the 2021-2022 season, cases peaked in mid-November 2021.[9] RSV is highly contagious and 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. Typically, adults will shed the virus for three to seven days following the infection. In general, infants shed the virus for up to 14 days in mild infections; however, in those with severe infection and aged less than six months, the virus may shed for up to three weeks. Additionally, immunocompromised individuals may shed for the virus for several months following infection.[10] 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.[10]

In most healthy individuals, RSV infection 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.[11] Non-pharmaceutical measures to prevent RSV infection include frequent handwashing, respiratory hygiene and cleaning contaminated surfaces such as door handles.[9] When high levels of RSV are known to be circulating, recommendations have been issued that people cocoon very young babies and avoid having them in large crowds or near people with a cold and respiratory symptoms.[12] In the hospital setting, RSV transmission can be prevented by managing patients with RSV on the same ward (that is, cohorting patients), use of gowns and gloves and restricting visiting.[9]

In Europe, as of 1 June 2024, there are three forms of passive immunisation approved for use in infants against RSV. Two of these, palivizumab and nirsevimab, are monoclonal antibodies while RSVpreF (Abrysvo®) is a maternal vaccine. For

adults, there are two vaccines, RSVpreF (Abrysvo®) and RSVPreF3 (Arexvy®),[13] which are authorised for use in adults aged 60 years and older.

Palivizumab (Synagis®) is a monoclonal antibody, authorised by the European Medicines Agency (EMA) in August 1999. It is administered by intramuscular (IM) injection at one-month intervals during the RSV season.[14] In Ireland, palivizumab is used for the prevention of serious lower respiratory tract disease in infants at highest risk of RSV disease.[15] In the first year of life, palivizumab prophylaxis is recommended for:

- infants born before 30 weeks', 0 day's gestation
- preterm infants with chronic lung disease (CLD) of prematurity (defined as birth at less than 32 weeks' gestation and a requirement for more than 21% oxygen for at least 28 days after birth)
- certain infants with hemodynamically significant heart disease, specifically those with acyanotic heart disease requiring medication for congestive cardiac failure and or moderate to severe pulmonary hypertension, and infants with cyanotic heart disease (in consultation with a cardiology specialist).

In the first year of life, palivizumab prophylaxis may also be considered in:

- infants with a pulmonary abnormality or neuromuscular disease that impairs their ability to clear upper airways secretions
- children younger than one year who will be profoundly immunocompromised during the RSV season.

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

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

In the second year of life, palivizumab prophylaxis may also be considered in:

- children who will be profoundly immunocompromised during the RSV season.[15]

Nirsevimab (Beyfortus®) is a long-acting monoclonal antibody, authorised by the EMA in October 2022.[16] It is administered as a single IM dose and is indicated for the prevention of RSV disease in neonates and infants during their first RSV season.

RSVpreF (Abrysvo®) is a maternal vaccine authorised by the EMA in August 2023.[17] It provides infants with protection against RSV-related lower respiratory tract disease from birth to six months of age through transplacental antibody transfer. It is indicated for administration as a single IM dose between 24 and 36 weeks of gestation. Abrysvo® is also approved for use in adults aged 60 years and older.

Additionally, RSVPreF3 (Arexvy®),[13] authorised by the EMA in June 2023, is another vaccine approved for use 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 updated recommendations to the Department of Health in Ireland regarding immunisation against RSV.[18] NIAC recommends the passive immunisation (immunity that occurs when a person is given antibodies rather than making them through their own immune system) of all infants against RSV during their first RSV season. They also recommend, that once available, nirsevimab should replace palivizumab for infants at high risk of severe disease and children who are currently eligible to receive palivizumab.[18] Regarding adults, NIAC recommends active immunisation of all adults aged 65 years and older with either RSVPreF3 or RSVpreF. Additionally, NIAC 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 will be limited to a restricted number of domains. Reviews of clinical effectiveness and safety will not be undertaken as part of this rapid HTA, due to the short timeline within which the information needs to be provided. Furthermore, while randomised controlled trial data are available, it is likely that the evidence relating to the clinical effectiveness and safety will evolve rapidly, given the recent authorisation of these technologies. Similarly, since this will inform an interim decision for one season, rather than a permanent change to the programme, a review of the cost effectiveness literature will not be undertaken. 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.

This protocol aims to present the methods for estimating the burden of disease associated with RSV in infants and adults, and assessing the costing implications associated with different immunisation strategies against RSV in Ireland for the 2025-2026 season.

1.2. Aims and objectives

The overarching aim of this rapid HTA is 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 is provided in the context of the clinical recommendations previously provided by NIAC to the Department of Health. With respect to the immunisation of infants and older adults against RSV in Ireland, the objectives (that is, terms of reference) for this assessment are 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 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.

1.3. Establishment of the Expert Advisory Group

An appropriately representative Expert Advisory Group (EAG) will be convened as a source of expertise to inform the interpretation of the evidence and development of the advice to the Minister for Health and HSE. This group will comprise nominees from a range of stakeholder organisations, including patient representation, healthcare providers and managers, as well as clinical, public health and methodological experts.

2. Description of technology and international practice

A description of the forms of RSV immunisation authorised for use (either by the EMA or the Health Products Regulatory Authority (HPRA) in Ireland) will be provided. A high-level comparison of the characteristics of the different forms of immunisation available will also be provided.

3. Review of international practice

A review of current RSV immunisation recommendations and immunisation programmes in EU/EEA countries and the UK will be undertaken. Data extracted will include a summary of the evidence underpinning the recommendation or policy decision (where available), with a particular focus on countries that have implemented an RSV immunisation programme (to include information on reimbursement of RSV vaccination).

4. Epidemiology and burden of disease

A comprehensive description of the epidemiology of RSV and burden of disease associated with RSV in the target population will be provided. This section will be informed by a review of national and international literature and databases.

RSV is a notifiable disease in Ireland under the Infectious Disease Regulations, and cases should be notified to the Medical Officer of Health. Notifications are reported using the Irish Computerised Infectious Disease Reporting system (CIDR).[19] RSV activity in Ireland is monitored by the Health Protection Surveillance Centre (HPSC).[9] RSV incidence will be estimated from data obtained from the HPSC. Data from the Hospitalised In-Patient Enquiry (HIPE) system will be sought to understand the nature of RSV hospitalisations (for example, complications of the disease, hospital length of stay and the average cost of admissions).[20] Cross sectional analyses of nationally representative datasets and individual studies will be used, if deemed appropriate. Where there is an absence of Irish data, the best available estimates will be derived from international literature. We will also describe the

uptake of palivizumab, a monoclonal antibody that is currently offered to children at high risk of RSV disease in Ireland. Data to inform palivizumab uptake will be sought from the HSE Primary Care Reimbursement Service (PCRS) and from relevant hospital pharmacies.

Data describing the uptake of other seasonal vaccines in Ireland will be used to inform the predicted uptake of immunisation against RSV. In the absence of national estimates related to antental uptake of COVID-19, influenza and pertussis vaccinations, available Irish studies reporting the uptake of these vaccinations will be summarised and used to inform the predicted uptake of immunisation against RSV in pregnant women. The HPSC report seasonal influenza and COVID-19 vaccination uptake data in Ireland, specifically for those aged 65 years and older. Trends in HPSC-reported vaccine uptake will be summarised and used to inform the predicted uptake of immunisation against RSV in older people. Estimates of the uptake of immunisation against RSV, identified from the review of international practice, will also be reported.

5. Costing analysis

The costing analysis will provide information for policy-makers regarding the potential affordability of immunisation against RSV in infants and older adults. It will estimate the potential cost to the HSE associated with implementing alternative immunisation programmes as a temporary measure for the 2025-2026 RSV season. In addition to the cost of the vaccines and monoclonal antibodies and the cost of their administration, potential costs relating to the expansion of the HSE Immunisation Programme (for example, information and promotional material) or required changes to organisational processes, if any, will be identified and considered as part of the costing analysis.

Data on the number of pregnant women will be sought from the Central Statistics Office (CSO). Data on the number of births within the RSV season and year-round will also be sought from the CSO. Data relating to the high-risk infant population who are eligible to receive palivizumab will be sought from the Primary Care Reimbursement Service (PCRS). Data on the total number of adults aged 65 years and older will be sought from the CSO.

6. Conclusion

In October 2023, NIAC issued recommendations to the Department of Health in Ireland regarding immunisation against RSV. Given the healthcare burden associated with RSV and the recent authorisation of nirsevimab, RSVpreF and RSVPreF3, many countries are considering changes to their immunisation programmes to include

immunisation against RSV. The aim of this rapid HTA is to provide advice to the Minister for Health and 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 is provided in the context of the clinical recommendations previously provided by NIAC to the Department of Health.

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