Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment of use of an enhanced inactivated influenza vaccine for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme

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About the Health Information and Quality Authority

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

Seasonal influenza is a contagious respiratory illness. In many cases, the disease is mild, with symptoms such as cough, fever, chills and fatigue. However, it can also result in serious complications, particularly in vulnerable groups such as young children, adults aged 65 years and older, pregnant women and those with medical conditions such as diabetes, asthma or heart disease. In the Northern Hemisphere, the influenza season commences in October and continues to May. The World Health Organization estimates that seasonal influenza can account for approximately 290,000 to 650,000 respiratory deaths annually worldwide.

Seasonal influenza may be prevented by annual influenza vaccination. In Ireland, those aged 65 years and older are one of the groups eligible to receive a free annual influenza vaccine through the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme. However, sometimes vaccine effectiveness can be suboptimal due to a mismatch between the content of the vaccine and the influenza strains circulating that year. Vaccine effectiveness may also be reduced due to an ageing or compromised immune system. Enhanced influenza vaccines have been developed in an attempt to increase vaccine effectiveness.

The purpose of this health technology assessment (HTA) is to inform a decision as to whether enhanced influenza vaccines should be funded as part of the HSE Seasonal Influenza Vaccination Programme, for those aged 65 years and older.

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

Dr Máirín Ryan

Deputy Chief Executive & Director of Health Technology Assessment

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*Until February 2024; ~From February 2024 until May 2024; ^From May 2024 to present.

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

Health Protection Surveillance Centre, HSE

Healthcare Pricing Office, HSE

Primary Care Reimbursement Service, HSE

Members of the Evaluation Team:

This report was led by staff in HIQA's HTA Directorate. The following individuals contributed to the management, technical writing or dissemination of this report:

Dr Karen Cardwell (Project lead), Ms Susan Ahern, Ms Aoife Bergin, Mr David Byrne, Ms Marie Carrigan, Dr Patricia Harrington, Ms Orla Jenkins, Dr Louise Larkin, Dr Carol McLoughlin, Ms Michelle O'Shea, Ms Allison Panaro, Dr Valerie Power, Dr Máirín Ryan, Ms Debra Spillane, Ms Dana Swanton, Dr Conor Teljeur, Dr Kieran Walsh.

Conflicts of Interest

Dr Hanlon and Dr Walkin are general practitioners who derive a small portion of their income from administration of vaccines.

Dr Keegan is a member of the Adult Immunisation Board. The Board is a scientific advisory board hosted by the University of Antwerp and the University of Florence and funded by an unrestricted grant from Vaccines Europe to cover travel and subsistence only. Vaccines Europe is a specialised vaccines group within the European Federation of Pharmaceutical Industries and Associations, the professional association of the innovative pharmaceutical industry in Europe.

There were no reported potential conflicts of interest for members of the Evaluation Team.

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 health technology assessment (HTA) to inform a policy decision by the Minister for Health in relation to whether enhanced inactivated influenza vaccines (IIVs) should be provided for adults aged 65 years and older as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme. This HTA aimed to assess the clinical effectiveness and safety of these vaccines relative to standard IIVs, as well as the cost effectiveness, budget impact, ethical and social aspects, and organisational implications associated with a switch from universal vaccination with a standard IIV to universal vaccination with an enhanced IIV in those aged 65 years and older.

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

- Influenza is a seasonal contagious respiratory viral illness. Although in many cases the symptoms are mild, some groups are at increased risk of severe disease. All population groups are impacted during influenza seasons, although proportions vary from one year to another, depending on the circulating viruses and population immunity.
- Annual vaccination is an important preventive measure to reduce the burden associated with seasonal influenza. Vaccine schedules internationally aim to reduce the burden of seasonal influenza typically through the selective vaccination of those at highest risk of severe disease.
- Available IIVs include standard trivalent IIVs (TIVs), standard quadrivalent IIVs (QIVs) and enhanced IIVs. Vaccine effectiveness may be reduced in older adults due to immunosenescence, a natural part of the ageing process. Enhanced IIVs aim to improve vaccine effectiveness relative to standard IIVs. These enhanced IIVs include:
    - adjuvanted IIV (aIIV) — IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response
    - high-dose IIV (HD-IIV) — IIV which contains a four-fold increase of haemagglutinin (HA) per strain (that is, 60µg) instead of 15µg of HA typically included in a standard dose IIV

  - vaccines manufactured using alternative substrates to the traditional egg-derived processes, thereby removing the possibility of strain mutation associated with egg-based propagation:
    - cell-based IIV (ccIIV) — IIV manufactured using mammalian cell-culture
    - recombinant HA IV (RIIV) — IIV manufactured using recombinant HA proteins.

- Three standard QIVs have been nationally authorised through the Health Products Regulatory Authority (HPRA), of which two were funded as part of the 2023-2024 HSE Seasonal Influenza Vaccination Programme.
- As of April 2024, three enhanced IIVs have been centrally authorised through the European Medicines Agency (EMA) and one enhanced IIV (HD-QIV) has been nationally authorised through the HPRA; none are marketed in Ireland.
- Ireland's National Immunisation Advisory Committee (NIAC) recommends an adjuvanted QIV (aQIV) for those aged 65 years and older, or a standard QIV if an aQIV is not available. Currently, no enhanced IIV is funded through the HSE Seasonal Influenza Vaccination Programme.
- Data on influenza vaccination programmes, funding for such programmes, and influenza vaccine policies were reviewed for each EU/EEA country and the UK. While each of these countries recommend influenza vaccination for those aged 65 years and older, they differ with respect to their funding policies and the types of vaccines used. Ten of the 31 countries were identified to fund an enhanced IIV for some or all of the target population.
- Irish influenza incidence data, for those aged 65 years and older, indicate that for the period 2010-2011 to 2022-2023:
  - There has been year-on-year variability in terms of notified influenza case rates (range: 25.0 to 718.5 per 100,000) as well as rates of laboratory-confirmed influenza-related hospital admissions (range: 6.7 to 352.1 per 100,000), hospital admissions with an intensive care unit (ICU) stay (range 0.9 to 16.9 per 100,000) and influenza-related mortality (range 1.7 to 24.9 per 100,000).
  - For the 2022-2023 season, provisional data indicate that the highest rate of notified cases (1,495.1 per 100,000), laboratory-confirmed influenza-related

hospital admissions (580.3 per 100,000), and influenza-related deaths (102.1 per 100,000) were in those aged 85 years and older.

  - While there is an apparent trend of increasing incidence over time, this may reflect changes in testing practices.

- For those aged 65 years and older, Irish public acute hospital data for the period 2010 to 2022 indicate there were, on average:

  - 441 (range: 14 to 1,407) discharges per annum with a primary diagnosis of influenza. The mean hospital length of stay (LOS) was nine days and the mean total bed days was 3,853 days per annum.

  - 38 (range: 10 to 84) discharges per annum with a primary diagnosis of influenza that included an ICU stay. The mean hospital LOS was eight days and the mean total bed days associated with these discharges was 290 days per annum.

  - 351 (range: 16 to 1,282) discharges per annum with a secondary diagnosis of influenza.

- The cost of acute hospital care was estimated using Diagnosis Related Groups (DRGs). The average cost of the DRGs related to influenza was approximately €6.03 million per annum in those aged 65 years and older.

- It is acknowledged that these data are likely an underestimate as not all influenza cases are tested and some hospital discharges may not be coded. As such, data relating to influenza-like-illness (ILI) consultations in those aged 65 years and older were used as an indication of the total burden on primary care (range: 263.4 to 1,062.6 per 100,000 for the winter period).

- The influenza-related morbidity and mortality observed are in the context of an existing well-established seasonal influenza immunisation programme which offers a standard IIV to everyone aged 65 years and older.

  - For the 2022-2023 season, the overall seasonal influenza vaccination uptake in those aged 65 years and older was 76.5%, with evidence that uptake increases with age.

  - It is not known what proportion of the observed morbidity and mortality occurs in those who were not vaccinated as vaccine records are not linked with laboratory or hospital data.

- To examine the effectiveness of standard influenza vaccines, pooled vaccine effectiveness (VE) estimates were calculated using published data from the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) groups in Europe. VE was considerably lower in adults aged 65 years and older (34.0%, 95% confidence interval (CI): 23.6 to 43.0) compared with adults aged 18 to 64 years (51.6%, 95% CI: 45.1 to 57.3), with the highest effectiveness observed in children aged less than 18 years (57.7%, 95% CI: 35.7 to 72.1).

- In March 2024, the European Centre for Disease Prevention and Control (ECDC) published an update of their 2020 systematic review of the effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in adults aged 18 years and older. The findings of this update were summarised and used to inform HIQA's assessment of the relative effectiveness and safety of these vaccines in adults aged 65 years and older.

    - The updated review included a total of 59 studies, of which 17 studies reported efficacy and or effectiveness data and 42 studies reported safety data. For primary efficacy and or effectiveness outcomes, included studies were limited to those that reported prevention of laboratory-confirmed influenza.

    - Overall, a limited number of studies were identified that provide low to moderate certainty evidence for the relative efficacy and effectiveness of the enhanced IIVs compared to standard IIVs in those aged 65 years and older. There is evidence of inconsistencies in the data and a paucity of data over multiple influenza seasons. Moreover, no head-to-head studies comparing the enhanced vaccines were identified and no study reported relative effectiveness data in relation to influenza-related death.

    - There is some evidence of improved outcomes with aIIVs and with HD-IIVs compared to standard IIVs. Specifically, there is evidence of a statistically significant reduction in:

        - influenza-associated hospitalisations for aIIV (rVE 59.2% (95% CI: 14.6 to 80.5)) based on the findings of a single observational study (n=512) over two consecutive seasons

        - laboratory-confirmed influenza for HD-IIV (rVE 24.2% (95% CI: 9.7 to 36.5) based on the results of a single randomised-controlled trial (RCT) (n=31,989) over two consecutive seasons.

- A larger evidence base is available on the safety of the enhanced vaccines. Based on low certainty evidence, there is no difference in the risk of serious vaccine-related events compared to standard IIVs. While three of the enhanced IIVs (aIIVs, HD-IIVs, and cc-IIVs) are associated with an increased risk of local and systemic reactions compared to standard IIVs, overall these vaccines generally appear to be well tolerated.

- The overall level of uncertainty of the comparative clinical effectiveness of the enhanced vaccines is too high to inform preferential advice for the use of one of these vaccines (aIIV and HD-IIV) over the other.

- A dynamic transmission model was developed that describes the transmission and incidence of notified cases of influenza in the general population in Ireland in an average influenza season. It incorporates both the current HSE Seasonal Influenza Vaccination Programme and the impact of switching from a standard IIV to an enhanced IIV for everyone aged 65 years and older.

- Given evidence of a statistically significant improvement in one or more clinical outcomes relative to standard IIV in a population aged 65 years and older, the model specifically assessed the following two enhanced IIVs:

  - high-dose inactivated influenza vaccine (HD-IIV)

  - adjuvanted inactivated influenza vaccine (aIIV).

- From the payer perspective, of the three strategies considered, and assuming that the standard IIV is procured at the ex-VAT (excluding value-added tax) list price of €10.99, it was estimated that:

  - A strategy based on aIIV dominated the existing strategy based on standard IIV, being less costly and more effective (more quality-adjusted life years (QALYs)) and would therefore be considered cost saving.

  - A strategy based on HD-IIV was both more costly and more effective than an aIIV-based strategy. The incremental cost-effectiveness ratio (ICER) for this comparison was estimated at €76,731 per QALY gained and therefore would be considered not cost effective at a willingness-to-pay (WTP) threshold of €45,000 per QALY.

  - At a WTP threshold of:

    - €20,000 per QALY, aIIV had the highest probability of being the cost-effective strategy (65.2%), followed by standard IIV (27.6%).

    - €45,000 per QALY, aIIV again had the highest probability of being the cost-effective strategy (55.4%), followed by HD-IIV (22.9%).

- The sensitivity analysis highlighted that the estimates of cost effectiveness were highly sensitive to a number of parameters including the relative costs of the enhanced IIVs (compared with standard IIV). Given the high degree of uncertainty, a number of scenario analyses were conducted where the relative costs of the vaccines were varied, both alone and in combination, to understand the impact on the ICERs. A decision rule was therefore developed which would allow the strategy providing the largest net monetary benefit to be identified by the National Immunisation Office (NIO) once the vaccine costs are known as part of any contract negotiations. At a WTP threshold of €20,000 per QALY, the results indicated that:
    - where the difference in unit cost between aIIV and standard IIV was €8 or less, a strategy with aIIV had the largest net monetary benefit
    - where the difference in unit cost between aIIV and standard IIV was €9 or more, a strategy with standard IIV had the largest net monetary benefit
    - where the difference in unit cost between aIIV and standard IIV was between €8 and €9, there remains a high degree of uncertainty as to whether a strategy with standard IIV or aIIV would generate the largest net monetary benefit
    - HD-IIV generated the largest net monetary benefit only where the difference in cost between it and aIIV was €9 or less and the cost of standard IIV was between €5 and €10.99.
- The estimated one-year incremental budget impact was a saving of €316,000 (95% CI: -5.1 million to 3.6 million) for the aIIV strategy and an increased cost of €11.3 million (95% CI: 0.7 to 22.1 million) for the HD-IIV strategy. These estimates are highly uncertain and assumed that standard IIVs are procured at an ex-VAT list price of €10.99 (which would suggest a current annual acquisition cost of €8.28 million (including VAT) for those aged 65 years and older based on 76% uptake).
    - Increased expenditure on procurement of the aIIV (€3.8 million) was offset by savings in the cost of hospitalisation (€4.1 million) due to the higher clinical effectiveness of aIIV (compared with standard IIV) in reducing influenza-related hospitalisation in those aged 65 years and older.

  - Increased spending on procurement of HD-IIV (€18.9 million) was partially offset by cost savings (€7.6 million) from reductions in hospitalisations, GP visits and prescription medications for those with GP visit or medical cards, due to the higher clinical effectiveness of HD-IIV, compared with standard IIV, in preventing influenza.

- The results demonstrated that the outcome of this economic evaluation is highly sensitive to the assumed relative unit costs of the adjuvanted, high-dose and standard IIVs. Given the lack of high certainty data to support preferential advice for the use of one of these vaccines over the other, the relative price of the vaccines should be a key consideration in a decision to offer an enhanced vaccine as part of the HSE Seasonal Influenza Vaccination Programme.

- Given that Ireland has a well-established nationally funded HSE Seasonal Influenza Vaccination Programme which currently funds universal vaccination for those aged 65 years and older, it is anticipated that organisational issues for the programme associated with any switch to an enhanced IIV for this cohort would be relatively minor and include:

  - an information campaign for the public, to clearly indicate the vaccine type provided and for whom it is intended, to educate individuals on the potential risk of complications from influenza, allay any concerns regarding the safety or efficacy of the vaccine, and enable informed consent.

  - updates to the educational material provided to GPs, pharmacists and front-line nursing staff to include information specific to the enhanced IIV given their important role both in vaccine administration and as a trusted information source regarding the immunisation programme. It is not expected that the updates would result in any additional resource use over that required by existing information campaigns for the influenza programme.

- There is evidence that provision of evidence-based information, knowledge and recommendations from healthcare professionals supports more positive beliefs towards vaccination and a willingness to receive an influenza vaccine. In addition, the provision of information around the burden of influenza in older adults and the potential for improved protection with the enhanced IIVs will help ensure vaccine decisions are evidence based and may increase an individual's perceived benefit from vaccination.
- At a population level, improved effectiveness with the enhanced IIVs could be considered to improve equity and would benefit community immunity, increasing protection for those who are not vaccinated. However, the healthcare budget is

finite and decisions regarding increased spending relating to a change of vaccine could impact the provision of other health technologies within the healthcare system. While there is uncertainty surrounding the parameter values, evidence from the economic evaluation indicate that use of aIIVs in those aged 65 years and older may represent the most efficient use of healthcare resources. This strategy would be more effective and less costly than the current strategy using standard IIVs although this finding is highly sensitive to the relative cost of these vaccines.

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

- Influenza is associated with substantial morbidity and mortality in adults aged 65 years and older with, on average, 441 (range: 14 to 1,407) hospital discharges with a primary diagnosis of influenza each year in Ireland for the period 2010 to 2022. This considerable burden exists in the context of an established HSE Seasonal Influenza Vaccination Programme, which currently offers a standard inactivated influenza vaccine (IIV), with an uptake of 76.5% in the 2022-2023 season, for those aged 65 years and older.
- The effectiveness of standard IIVs can be suboptimal in certain population groups. As a result, enhanced influenza vaccines have been developed that aim to improve vaccine effectiveness. These include adjuvanted IIVs (aIIVs), high-dose IIVs (HD-IIVs), cell-based IIVs (cc-IIVs), and recombinant IIVs (RIIVs).
- Compared with standard IIVs, in those aged 65 years and older:
    - There is no evidence of a difference in the risk of serious vaccine-related events. Three of the enhanced IIVs (aIIVs, HD-IIVs, and cc-IIVs) are associated with an increased risk of local and systemic reactions; however, these vaccines are generally well tolerated with a large evidence base to support their safety.
    - The overall evidence base for efficacy and effectiveness is limited due to the small number of studies and a paucity of data over multiple seasons. There is some evidence of improved outcomes with aIIVs and HD-IIVs, with these findings derived from single studies. Due to the variability of seasonal influenza, a single study may misrepresent the 'on average' vaccine effectiveness.
- Considering the limitations of the vaccine effectiveness data and that the relative costs of the vaccines are unknown, the evaluation of cost effectiveness

is subject to substantial uncertainty. Given the assumptions of the economic model:

  - A strategy based on aIIV dominated the existing strategy based on standard IIV, being less costly and more effective, and would therefore be considered cost saving.
  - A strategy based on HD-IIV was both more costly and more effective than an aIIV-based strategy. The incremental cost-effectiveness ratio (ICER) for this comparison was estimated at €77,000 per quality-adjusted life year (QALY) gained, and therefore would be considered not cost effective at a willingness to pay (WTP) threshold of €45,000 per QALY.
  - At a WTP threshold of €20,000 and €45,000 per QALY, aIIV had the highest probability of being the cost-effective strategy (65% and 55%, respectively).

- The estimated one-year incremental budget impact was a saving of €316,000 for an aIIV-based strategy and an increased cost of €11.3 million for a HD-IIV-based strategy. These estimates are highly uncertain and assumed that standard IIVs are procured at an ex-VAT list price of €10.99 (which would suggest a current annual acquisition cost of €8.28 million (including VAT) based on 76% uptake).
- The overall level of uncertainty of the comparative clinical effectiveness of the enhanced vaccines is too high to inform preferential advice for the use of one these vaccines (aIIV or HD-IIV) over the other. The relative price of the vaccines should therefore be a key consideration in a decision to offer an enhanced vaccine.
- Ongoing evaluation of the HSE Seasonal Influenza Vaccination Programme is important to ensure the best possible clinical benefit for the resources allocated. This could be enhanced by improved linkage of influenza vaccination records with laboratory and hospital data.

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 HTA was to inform a decision as to whether enhanced inactivated influenza vaccines (IIVs) should be funded as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme for those aged 65 years and older. This HTA considered the following domains:

- description of technology
- epidemiology and burden of disease
- clinical effectiveness and safety
- cost effectiveness
- budget impact analysis
- organisational issues
- ethical, patient and social considerations.

Background

Following a request from the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a HTA in relation to whether enhanced IIVs should be reimbursed for adults aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme. Ireland's National Immunisation Advisory Committee (NIAC) recommends an adjuvanted quadrivalent inactivated influenza vaccine (aQIV) for those aged 65 years and older, or a standard QIV if an aQIV is not available. Currently, no enhanced IIV is funded through the HSE Seasonal Influenza Vaccination Programme.

Description of the technology

Seasonal influenza is characterised by respiratory and systemic symptoms, including fever, malaise, myalgia, headache, sore throat and nasal congestion. Treatment consists of antipyretics, adequate fluid intake and rest. However, certain individuals have an increased risk of severe disease (for example, those aged 65 years and older and those with certain medical conditions), and may require hospitalisation. Annual vaccination is an important preventive measure to reduce the burden

associated with seasonal influenza. Vaccine schedules internationally aim to reduce the burden of seasonal influenza through the selective vaccination of those at highest risk of severe disease. Available inactivated influenza vaccines (IIVs) include standard trivalent IIVs (TIVs), standard quadrivalent IIVs (QIVs) and enhanced IIVs. Enhanced IIVs were developed to improve vaccine effectiveness and include:

- adjuvanted IIV (aIIV) – IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response
- high-dose IIV (HD-IIV) – IIV which contains a four-fold increase of hemagglutinin (HA) per strain, (that is, 60µg) instead of 15µg of HA typically included in a standard dose IIV
- vaccines manufactured using alternative substrates to the traditional egg-derived processes, thereby removing the possibility of strain mutation associated with egg-based propagation
    - cell-based IIV (ccIIV) – IIV manufactured using mammalian cell culture
    - recombinant HA IV (RIIV) – IIV manufactured using recombinant HA proteins.

Three standard QIVs have been nationally authorised through the Health Products Regulatory Authority (HPRA), of which two were funded as part of the 2023-2024 HSE Seasonal Influenza Vaccination Programme. As of April 2024, three enhanced IIVs have been centrally authorised through the European Medicines Agency (EMA) and one enhanced IIV (HD-QIV) has been nationally authorised through the HPRA; however, none are currently marketed in Ireland. In March 2024, the European Medicines Agency (EMA) Emergency Task Force (ETF) issued a recommendation regarding the replacement of quadrivalent influenza vaccines with trivalent vaccines in the EU. This Task Force recommendation was on the foot of the February 2024 update report from the World Health Organization (WHO) which recommended the removal of antigens for the B/Yamagata lineage from seasonal influenza vaccines. Both the EMA and WHO reports highlighted that there has been no confirmed detection of the naturally occurring B/Yamagata virus since March 2020 and, as such, the relevance of vaccinating against this lineage has been questioned. Moreover, the reports highlighted the potential that live attenuated virus vaccines (LAIVs) containing the B/Yamagata antigen could pose a risk of the lineage being reintroduced into humans. The EMA ETF have recommended that, ideally, the antigens of the B/Yamagata lineage should be removed from LAIVs for the 2024-2025 influenza season. For IIVs (which are the subject of this HTA), they have recommended that the B/Yamagata lineage should be removed for the 2025-2026

season as there is no public health concern requiring an immediate transition, and vaccine availability is of primary importance.

Seasonal influenza vaccination policies for the EU/EEA and UK were reviewed for the 2023-2024 influenza season. All EU/EEA countries and the UK recommended influenza vaccination for those aged 65 years and older, although countries differed with regard to their funding policies and types of vaccine used. In total, 24 of 31 countries fully fund influenza vaccinations, three countries partly fund influenza vaccinations, three countries do not fund influenza vaccinations and funding in one country varies by region. Considering enhanced IIVs, 10 countries fund this vaccine type for some or all of their target population. Six of these countries specifically fund a HD-QIV only, one funds an aQIV only, one funds an aQIV, HD-QIV or ccQIV, one funds an aQIV, RIV4 or ccQIV, and one funds all four enhanced IIV types. In addition, five countries (Belgium, Liechtenstein, Norway, Portugal and Sweden) restrict availability of enhanced IIVs to subgroups of the target population, for example, to those aged 75 years or older, or those living in long-term care facilities. Three of these countries (Belgium, Liechtenstein and Portugal) fund enhanced IIVs, Norway does not, while in Sweden the funding varies by region.

Epidemiology and burden of disease

Influenza is a contagious respiratory disease and immunity provided by vaccines is temporary, making a large proportion of the population susceptible to infection each season. While all population groups are impacted during influenza seasons, the proportions vary from one year to another, depending on the circulating viruses and population immunity. Although in many cases the symptoms of illness are mild, complications can occur. Data on the epidemiology and burden of influenza in Ireland were sourced from the Health Protection Surveillance Centre (HPSC), which provided influenza incidence data for the period 2010-2011 to 2022-2023, and the Hospital Inpatient Enquiry System (HIPE), which provided hospital utilisation data per calendar year for the period 2010 to 2022. Estimates from the seasons influenced by COVID-19, that is, 2020-2021 and 2021-2022, were excluded as these data were not considered to be representative. From 2010-2011 to 2022-2023, HPSC data for adults aged 65 years and older indicated that there has been considerable year-on-year variability in the rates of notified influenza cases (range: 25.0 to 718.5 per 100,000), laboratory-confirmed influenza-related hospital admissions (range: 6.7 to 352.1 per 100,000), hospital admissions with an intensive care unit (ICU) stay (range: 0.9 to 16.9 per 100,000) and influenza-related mortality (range: 1.7 to 24.9 per 100,000).

HPSC data for a number of indicators were also disaggregated by five-year age band, which indicated that burden generally increases with age, with substantial

year-on-year variability within each age band. Provisional data for the 2022-2023 season reported the following rates:

- notified influenza cases ranged from 381.6 per 100,000 among adults aged 65 to 69 years to 1,495.1 per 100,000 in those aged 85 years and older
- laboratory-confirmed influenza-related hospital admissions ranged from 137.8 per 100,000 among adults aged 65 to 69 years to 580.3 per 100,000 in those aged 85 years and older
- laboratory-confirmed influenza-related hospital admissions requiring an ICU stay ranged from 3.7 per 100,000 among adults aged 80 to 84 years to 19.1 per 100,000 in those aged 75 to 79 years
- Influenza-related deaths ranged from 7.1 per 100,000 among adults aged 65 to 69 years to 102.1 per 100,000 in those aged 85 years and older.

Since not all cases of influenza are laboratory-confirmed, data on influenza-like illness (ILI) consultations in those aged 65 years and older were obtained from the HPSC and used to represent the total burden on primary care. For the period 2010-2011 to 2022-2023 (excluding the seasons influenced by COVID-19), the ILI-consultation rate ranged from 263.4 to 1,062.6 per 100,000 for the winter period. For the 2022-2023 season alone, the ILI-consultation rate was 899.6 per 100,000 (n=331 cases) in the winter period.

The HIPE data showed substantial variability in relation to the number of discharges, hospital length of stay (LOS) and total bed days over time, between 2010 and 2022. For those aged 65 years and older, the data show that, on average, there were:

- 441 (range: 14 to 1,407) discharges per annum with a primary diagnosis of influenza. The mean LOS was nine days and the mean total bed days was 3,853 days per annum.
- 38 (range: 10 to 84) discharges per annum with a primary diagnosis of influenza that included an ICU stay. The mean hospital LOS was eight days and the mean total bed days associated with these discharges was 290 days per annum.
- 351 (range: 16 to 1,282) discharges per annum with a secondary diagnosis of influenza.

In terms of the economic burden associated with influenza illness, the cost of acute hospital cases was estimated using Diagnosis Related Groups (DRGs). The average cost of the DRGs related to influenza was approximately €6.03 million per annum in those aged 65 years and older. These estimates of the morbidity and mortality

burden associated with influenza are in the context of an existing HSE Seasonal Influenza Vaccination Programme which offers a standard QIV to those aged 65 years and older. For the 2022-2023 season, vaccination coverage in this cohort was 76.5%, with evidence that uptake increases with age. However, it is not known what proportion of the observed morbidity and mortality occurred in those who were not vaccinated. It is also acknowledged that the data presented in this chapter are likely an underestimate of the true burden of influenza, as not all influenza cases are tested, while some hospital discharges may not be coded. Although there was an apparent trend of increasing incidence over time, this may reflect changing testing practices.

Review of clinical effectiveness and safety

Enhanced IIVs aim to improve the effectiveness of vaccination against influenza compared with standard IIVs. This is particularly relevant in older adults, in whom vaccine effectiveness (VE) may be reduced due to immunosenescence, a natural part of the ageing process. In March 2024, the European Centre for Disease Prevention and Control (ECDC) published an update of their 2020 systematic review of the effectiveness and safety of enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in adults aged 18 years and older. The findings of this systematic review were used to inform HIQA's assessment of the effectiveness and safety of specified enhanced IIVs in adults aged 65 years and older.

In total, 59 studies were included in the updated review; 17 studies reported efficacy and or effectiveness data and 42 studies reported safety data. For primary efficacy and or effectiveness outcomes, included studies were limited to those that reported prevention of laboratory-confirmed influenza. The four types of enhanced IIVs for which data were identified in the review were MF59® aIIVs, HD-IIVs, ccIIVs and RIIVs. No study reported effectiveness data in relation to influenza-related death for any of these vaccines.

Compared with standard IIVs, MF59® aIIVs may or may not reduce laboratory-confirmed influenza infection, as the relative VE (rVE) ranged from 19% (95% CI: -10 to 41) in one non-randomised study of interventions (NRSI) among adults aged 60 years and older, to between 30% (95% CI: -83 to 73) and 42% (95% CI: -8 to 69), based on two NRSIs among adults aged 65 years and older. MF59® aIIVs significantly reduced laboratory-confirmed influenza-related hospitalisations, based on an rVE 59.2% (95% CI: 14.6 to 80.5) compared with standard IIVs from one NRSI in adults aged 65 years and older. In terms of the safety of aIIVs compared with standard IIVs, there was no significant difference in the relative risk (RR) of serious adverse events (SAEs), based on a RR of 0.95 (95% CI: 0.19 to 4.72) from

three RCTs in adults aged 65 years and older. However, aIIVs were associated with a significantly increased risk of fever (RR 1.95, 95% CI: 1.35 to 2.80) and pain at the injection site (RR 1.94, 95% CI: 1.58 to 2.40) compared with standard IIVs.

Compared with standard IIVs, HD-IIVs significantly reduced laboratory-confirmed influenza infection, based on an rVE of 24.2% (95% CI: 9.7 to 36.5%) from one RCT in adults aged 65 years and older. There was no significant difference in laboratory-confirmed influenza-related hospitalisations, based on an rVE of 27% (95% CI: -1 to 48) for HD-IIVs compared with standard IIVs, from one NRSI in adults aged 65 years and older. In terms of the safety of HD-IIVs compared with standard IIVs, there was no significant difference in the RR of SAEs, based on a RR of 1.02 (95% CI: 0.42 to 2.46) from six RCTs, of which five related to adults aged 65 years and older. However, HD-IIVs were associated with an increased RR of headache (RR 1.25, 95% CI: 1.13 to 1.40), fever (RR 1.78, 95% CI: 1.25 to 2.54), pain at injection site (RR 1.52, 95% CI: 1.29 to 1.80), and swelling at injection site (RR 1.85, 95% CI: 1.27 to 2.71), compared with standard IIVs.

Compared with standard IIVs, ccIIVs did not significantly reduce laboratory-confirmed influenza infection, as the rVE ranged from -5.8% (95% CI: -36.1 to 17.7) to 21.4% (95% CI: -7.3 to 42.4) across two NRSIs in adults of mixed age ranges. Compared with standard IIVs, ccIIVs did not significantly reduce laboratory-confirmed influenza-related hospitalisation, based on an rVE of 8.5% (95% CI: -75.9 to 52.3) from one NRSI in adults aged 18 years and older. In terms of the safety of ccIIVs, there was no significant difference in the RR of SAEs compared with standard IIVs, based on a RR of 0.39 (95% CI: 0.02 to 9.49) from one RCT in adults aged 50 years and older. However, ccIIVs were associated with a significantly increased RR of pain at injection site (RR 1.19, 95% CI: 1.03 to 1.37) compared with standard IIVs.

Compared with standard IIVs, RIIVs significantly reduced laboratory-confirmed influenza infection, based on an rVE of 30% (95% CI: 10 to 47) from one RCT in adults aged 50 years and older. However, subgroup analysis by age indicated an rVE of 17% (95% CI: -20 to 43) in those aged 65 years and older. Compared with standard IIVs, RIIVs did not significantly reduce laboratory-confirmed influenza-related hospitalisations as the rVE ranged from -7.3% (95% CI: -52.1 to 24.4) for those aged 18 to 49 years to 16.3% (95% CI: -8.7 to 35.5) for those aged 50 to 64 years, based on one RCT in adults. In terms of the safety of RIIVs, there was no significant difference in the RR of SAEs compared with standard IIVs (RR 3.04, 95% CI: 0.32 to 29.10) based on two RCTs in adults aged 18 to 64 years. There was no significant difference reported for systemic or local adverse events observed with RIIVs compared with standard IIVs.

Overall, while the evidence on the rVE of enhanced IIVs compared with standard IIVs is limited, there is some evidence of a statistically significant reduction in influenza-related hospitalisations with aIIVs and for a statistically significant reduction in laboratory-confirmed influenza with HD-IIVs. The findings for these two vaccine types could be considered applicable to adults aged 65 years and older, based on the availability of evidence specifically relating to this age group. The applicability of the findings relating to ccIIVs and RIIVs is less clear, with no evidence of a statistically significant improvement in outcomes in this cohort. While the certainty of evidence was generally low, a larger evidence base is available on the safety of these vaccines. Overall, influenza vaccines are well tolerated. Serious adverse events are rare with both standard and enhanced IIVs, with no evidence of an increased risk of vaccine-related SAEs for any of the four enhanced IIVs considered. However, an increased risk of systemic and or local adverse events was reported for three of the enhanced IIVs (aIIV, HD-IIV, ccIIV). While more common, these local and systemic events were typically mild, transient and self-limiting.

Review of methodology for economic modelling studies of inactivated influenza vaccinations

The most recent systematic review of economic modelling studies of seasonal influenza vaccination in high-income countries was published in 2022, based on a literature search conducted up to 2020. To establish and assess the most up-to-date international evidence on approaches taken to the economic modelling of vaccination with an IIV in adults aged 65 years and older, a rapid review of studies published since 2020 was undertaken.

Nineteen additional studies were identified in the rapid review, 15 of which were conducted in EU/EEA countries. Fifteen of the included studies were funded by industry, three were conducted using government research funding and one received EU funding.

To estimate the impact of vaccination, 10 studies used static decision tree Markov models, seven studies incorporated decision tree economic models with dynamic transmission models, one study used a state transmission simulation model and one study described the model used as a static decision analytic model (but did not specify the model type). The majority of studies conducted their analyses over a short time horizon of one year or less. There was variation in the values of absolute VE against influenza across studies, with more consistency observed where rVE was used.

Seven studies adopted a dual perspective (considering both the healthcare and societal perspective) in the base-case analysis when evaluating the cost effectiveness of vaccination strategies, while eight studies considered the healthcare

perspective only. Two additional studies adopted a societal perspective in the base-case analysis, including the payer perspective in their scenario analyses. Two studies did not clearly report the perspective taken in their assessment of the impact of vaccination.

A critical appraisal of included studies was undertaken. There were some concerns with the structure, data and consistency of the identified models, the appropriateness of the choice of model, the comprehensiveness of the assessment of uncertainty, and the level of detail provided for the reporting of parameter data.

This rapid review identified several notable modelling features for consideration when developing an economic model of universal vaccination with an enhanced IIV in adults aged 65 years and older, all of which were considered in the development of a de novo economic model of seasonal influenza vaccination for Ireland.

Economic evaluation

A dynamic transmission model was developed that described the transmission and incidence of notified influenza in the general population in Ireland, incorporating both the current HSE Seasonal Influenza Vaccination Programme and the impact of switching from a standard IIV to an enhanced IIV for those aged 65 years and older. Given evidence of a statistically significant improvement in one or more clinical outcomes relative to a standard IIV in populations aged 65 years and older, the model specifically assessed two enhanced IIVs: aIIVs and HD-IIVs.

Three alternative vaccination strategies were assessed:

- current HSE Seasonal Influenza Vaccination Programme with a standard IIV administered to those aged 65 years and older
- current HSE Seasonal Influenza Vaccination Programme with an aIIV administered to those aged 65 years and older
- current HSE Seasonal Influenza Vaccination Programme with a HD-IIV administered to those aged 65 years and older.

From the payer perspective, a strategy based on an aIIV was estimated to dominate the existing strategy based on a standard IIV, being less costly and more effective (more quality-adjusted life years (QALYs)). A strategy based on a HD-IIV was both more costly and more effective than an aIIV-based strategy. The incremental cost-effectiveness ratio (ICER) for this comparison was estimated at €76,731 per QALY gained and therefore would be considered not cost effective at a willingness-to-pay (WTP) threshold of €45,000 per QALY. At a WTP threshold of €20,000 per QALY, an aIIV-based strategy had the highest probability of being the cost-effective strategy,

followed by a standard IIV-based strategy (65.2% and 27.6%, respectively). At a WTP threshold of €45,000 per QALY, an aIIV-based strategy again had the highest probability of being the cost-effective strategy, followed by a HD-IIV-based strategy (55.4% and 22.9%, respectively).

The sensitivity analysis highlighted that the cost-effectiveness results were highly sensitive to a number of parameters including the relative costs of the enhanced IIVs, compared with standard IIVs. Given this uncertainty, a number of scenario analyses were conducted where the relative costs were varied, both alone and in combination, to understand the impact on the ICERs. These analyses demonstrated that the findings were largely robust with the exception of the uncertainty over vaccine prices. A decision rule was therefore developed which would allow the strategy providing the largest net monetary benefit to be identified by the National Immunisation Office (NIO) once the vaccine costs are known as part of any contract negotiations. At a WTP threshold of €20,000 per QALY, the results indicated that:

- where the difference in unit cost between an aIIV and standard IIV was €8 or less, a strategy with an aIIV had the largest net monetary benefit
- where the difference in unit cost between an aIIV and standard IIV was €9 or more, a strategy with a standard IIV had the largest net monetary benefit
- where the difference in unit cost between an aIIV and standard IIV was between €8 and €9, there remains a high degree of uncertainty as to whether a strategy with a standard IIV or aIIV would generate the largest net monetary benefit
- HD-IIV generated the largest net monetary benefit only where the difference in cost between it and an aIIV was €9 or less and the cost of a standard IIV was between €5 and €10.99

The one-year incremental budget impact of strategies based on an aIIV and HD-IIV, compared with a standard IIV, were -€316,000 (95% CI: -5.1 million to 3.6 million) and €11.3 million (95% CI: 0.7 to 22.1 million), respectively. For an aIIV-based strategy, increased expenditure on procurement of the vaccine (€3.8 million) was offset by savings in the cost of hospitalisation (€4.1 million) due to the higher clinical effectiveness of an aIIV, compared with a standard IIV, in reducing influenza-related hospitalisations in those aged 65 years and older. Considering a HD-IIV-based strategy, increased spending on procurement of this vaccine (€18.9 million) was partially offset by cost savings (€7.6 million) from reductions in hospitalisations, GP visits and prescription medication for those with GP visit or medical cards, due to the higher clinical effectiveness of a HD-IIV, compared with a standard IIV, in preventing influenza. The budget impact estimates were also subject to a high

degree of uncertainty and the scenario analysis again highlighted that the results are highly sensitive to changes in the relative costs of the vaccines.

This modelling study is subject to a number of limitations. As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values. However, sensitivity and scenario analyses demonstrated that the findings are largely robust, with the exception of the uncertainty regarding vaccine prices. This should therefore be a key consideration in any decision-making and in procurement negotiations with vaccine manufacturers.

Organisational issues

Since the HSE Seasonal Influenza Vaccination Programme currently provides universal vaccination with a standard IIV for adults aged 65 years and older, it is anticipated that organisational issues associated with any switch to an enhanced IIV for the programme would be relatively minor. There is no expected impact on resources related to staff or vaccine storage and handling given that the change would be limited to the vaccine type.

While there is uncertainty in relation to the cost and relative costs of the standard and enhanced IIVs, it is expected that there would be an increased vaccine acquisition cost associated with any change to an enhanced IIV. This increased cost may be partially or completely offset by a reduced healthcare utilisation associated with influenza.

An information campaign for the public would be an important component of any change to the national immunisation schedule in order to educate individuals on the potential risk of complications from influenza, allay any concerns regarding the safety and efficacy of the vaccine, and to enable informed consent. To support such a public awareness campaign, consideration would also need to be given to updating the educational material provided to GPs, pharmacists and front-line nursing staff, given their important role both in vaccine administration and as a trusted information source for other vaccines given as part of the immunisation programme. It is not expected that such updates would result in additional resource use over that required by existing information campaigns for the influenza programme.

The HPSC reports annually on vaccination uptake. Vaccination of those aged 65 years and older with an enhanced IIV, instead of a standard IIV, will not result in any changes to the monitoring and evaluation of the influenza programme. It is not known if a switch to an enhanced IIV would lead to a change in vaccine uptake.

Ethical, patient and social considerations

The proposed change to the existing HSE Seasonal Influenza Vaccination Programme is limited to a change of vaccine type, from a standard IIV to an enhanced IIV. As such, the ethical issues relating to a change in the type of vaccine offered to people aged 65 years and older were considered. That being said, the obligation of governments to protect the health and wellbeing of citizens must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive.

Seasonal influenza in adults aged 65 years and older is associated with substantial burden on these individuals and healthcare services. This is in spite of an existing HSE Seasonal Influenza Vaccination Programme which offers a (free at the point of delivery) standard IIV to this cohort. The purpose of vaccination is to prevent or reduce the spread and severity of infectious disease. Evidence of improved outcomes specific to a population aged 65 years and older was available for two of the four enhanced IIVs considered in this HTA. Relative to standard IIVs, there is low-moderate certainty of evidence of a statistically significant reduction in laboratory-confirmed influenza infection and influenza-related hospitalisations with HD-IIVs and aIIVs, respectively. Serious adverse events are rare, such that the safety profile of enhanced IIVs is considered acceptable and relatively comparable to that of standard IIVs. Mild systemic and local reactions are relatively common; an increased risk of systemic and or local adverse reactions was reported with three of the enhanced IIVs considered (aIIVs, HD-IIVs and ccIIVs), although it is noted that these are typically transient and self-limiting.

There is evidence that provision of evidence-based information, knowledge and recommendations from healthcare professionals supports more positive beliefs towards vaccination and a willingness to receive an influenza vaccine. Provision of information around the burden of influenza in older adults and the potential for improved protection with the enhanced IIVs will help ensure vaccine decisions are evidence based and may increase an individual's perceived benefit from vaccination. At a population level, improved effectiveness with the enhanced IIVs would benefit community immunity (also known as herd immunity), increasing protection for those who are not vaccinated.

The healthcare budget is finite and decisions regarding increased spending relating to a change of vaccine could impact the provision of other health technologies within the healthcare system. While there is uncertainty surrounding the parameter values, evidence from the economic evaluation indicates that use of aIIVs in those aged 65 years and older may represent the most efficient use of healthcare resources. This strategy would be more effective and less costly than the current strategy using standard IIVs, although again it is noted that these results are highly sensitive to the relative unit cost of the vaccines.

Conclusions

In Ireland, the substantial burden associated with influenza in those aged 65 years and older is in the context of an existing universal vaccination programme offering standard IIVs, for which uptake was almost 77% in 2022-2023.

Based on the identification and availability of evidence specifically relating to adult populations aged 65 years and older, the findings of an updated systematic review of enhanced IIVs indicate that HD-IIVs and aIIVs could be more effective than standard IIVs in reducing cases of laboratory-confirmed influenza and or influenza-related hospitalisations, albeit with an increased relative risk in local and systemic adverse events such as headache, fever, pain at injection site and swelling at injection site.

Based on an economic evaluation of three potential influenza vaccination strategies in Ireland, a strategy based on an aIIV was estimated to dominate the existing strategy based on a standard IIV, being less costly and more effective, and would therefore be considered cost saving. A strategy based on a HD-IIV was estimated to be more effective than an aIIV-based strategy, but also more costly and therefore would not be considered cost effective at a WTP of €45,000.

The results of the economic evaluation demonstrated that the cost effectiveness and budget impact were highly sensitive to the assumed relative unit costs of the vaccines and should be a key consideration in any decision-making and in procurement negotiations with vaccine manufacturers.

Plain language summary

Influenza, or the flu, is a virus that infects the lungs and upper airways (windpipe, throat, mouth and nose). The flu virus spreads every winter. Some people recover quickly from the flu while others may get very sick and need hospital care. In serious cases, people can die from the flu, especially older people and those with underlying conditions. The best protection against the flu is to get the annual flu vaccine. Vaccination can help prevent the flu while those who still get the flu after being vaccinated usually have milder symptoms and recover faster. The flu virus changes over time, so the vaccine is updated each year, and people need to get it annually for ongoing protection.

As people get older, their immune systems become weaker and are less able to fight infections. People's response to vaccines also reduces. This means that vaccines may be less effective in older people. To help with this, enhanced flu vaccines have been developed. These include:

- adjuvanted flu vaccines, which contain an extra ingredient that boosts the immune response compared with standard vaccines
- high-dose flu vaccines, which have four times as much of the ingredients that trigger the immune response compared with standard vaccines.

In Ireland, a free annual flu vaccine is provided by the Health Service Executive (HSE) to certain groups of people and those who are at increased risk of developing severe illness from flu. Those at increased risk of severe illness include people aged 65 years and older. Currently, only standard flu vaccines are offered to this age group through the HSE Seasonal Influenza Vaccination Programme. However, the National Immunisation Advisory Committee (NIAC) has recommended an enhanced (adjuvanted) flu vaccine for those aged 65 years and older.

The Department of Health asked the Health Information and Quality Authority (HIQA) to look at the impact of making enhanced flu vaccines available to everyone aged 65 years and older. HIQA reviewed the evidence of how effective and safe enhanced flu vaccines are for older people. HIQA also considered the cost and whether it would be an efficient use of HSE resources. In addition, HIQA looked at the organisational, social and ethical impact of providing enhanced flu vaccines to adults aged 65 years and older through the HSE Seasonal Influenza Vaccination Programme.

HIQA looked to see what other European countries recommend for adults aged 65 years and older. HIQA reviewed evidence from 31 countries, all of which were found to recommend annual flu vaccination for this age group, but which differed in the type of vaccine and funding. HIQA found that 10 countries provide enhanced flu

vaccines for free to some or all older people. In five countries, these enhanced flu vaccines are free only for certain groups, such as those aged 75 or older, or those living in care homes. The most common enhanced vaccines offered in European countries are high-dose vaccines, followed by adjuvanted vaccines.

The number of people aged 65 years and older diagnosed with the flu and the number who require hospitalisation varies every year. In Ireland, these numbers have increased over time, as the number of people in this age group has increased. More testing is also being done in recent years and this may explain some of the increase in the number of people diagnosed with the flu. During the 2022 to 2023 flu season, over 4,500 people aged 65 and older were diagnosed with the flu. Nearly 1,800 were hospitalised, 70 needed ICU treatment, and 159 people died. Among older people, those aged 85 and older are more likely to be diagnosed with the flu and are more likely to be hospitalised. These hospitalisation and diagnoses data demonstrate the ongoing impact of flu on people and the healthcare system. Importantly, they are in the context of an existing vaccination programme where nearly eight out of every 10 people in this age group take up the vaccine that is offered. This highlights the need for better vaccines and the importance of high vaccine uptake.

HIQA looked at evidence of the safety and effectiveness of enhanced vaccines for people aged 65 years and older. This work was based on a report from the European Centre for Disease Prevention and Control, from March 2024. Overall, studies showed that adjuvanted vaccines may be more effective than standard vaccines in preventing hospitalisation due to flu in older adults High-dose vaccines may be more effective than standard vaccines in preventing flu cases in this age group. The effectiveness of other enhanced flu vaccines in older adults was unclear as the studies included people of different ages. In terms of safety, flu vaccines are generally safe and well tolerated. Serious adverse events are rare with both standard and enhanced flu vaccines. However, some side effects such as headache, pain at the injection site, or fever are more common with a number of the enhanced vaccines, but these are usually mild and short-lived.

In Ireland, over 800,000 adults aged 65 and older are offered a free flu vaccine each year through the HSE Seasonal Influenza Vaccination Programme. Currently the programme offers a standard flu vaccine to this age group. HIQA assessed whether switching to an enhanced flu vaccine for this age group would be a good use of HSE resources. In the economic evaluation, HIQA only included those enhanced vaccines for which we had found evidence that they may be more effective than standard vaccines. Accordingly, HIQA assessed the added benefits and costs of switching to an adjuvanted flu vaccine or a high-dose flu vaccine as part of the annual flu vaccination programme.

HIQA estimates that switching to an adjuvanted flu vaccine for those aged 65 and older would likely be the best use of resources. Although the vaccine may cost more, it would likely reduce the burden of flu and could save the HSE money by reducing hospitalisations. Replacing the standard flu vaccine with a high-dose vaccine could be an even more effective strategy, but it would likely cost the HSE more overall, as the higher vaccine price would only be partly offset by savings. The best value option would depend on the price the HSE has to pay for each type of vaccine, but these prices are confidential.

Since Ireland already has a seasonal flu vaccination programme for those aged 65 years and older, changing the type of vaccine offered would be expected to have very little impact on how the programme is organised. If a decision is made to change from a standard to an enhanced flu vaccine, it would be important to inform the public and healthcare professionals about the change. Clear information should be provided on the potential added benefits of the enhanced vaccine. While the side effects of flu vaccines are usually mild and short-lived, it should be explained that these can occur more frequently with the some of the enhanced vaccines. This information would support healthcare professionals in providing trustworthy advice and ultimately helping people to make informed decisions about vaccination.

In summary, offering an adjuvanted or high dose flu vaccine to people aged 65 and older instead of a standard vaccine would likely reduce the burden of flu. Whether such a switch would represent a good use of HSE resources would depend on the price the HSE has to pay for one of these enhanced vaccines compared with the standard flu vaccine.

List of abbreviations used in this report

ACER	average cost-effectiveness ratio
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
AOM	acute otitis media
BIA	budget impact analysis
CAD	Canadian dollar
CAP	community acquired pneumonia
CBA	cost-benefit analysis
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHO	Community Healthcare Organisation
CI	confidence interval
CIDR	Irish Computerised Infectious Disease Reporting System
COPD	chronic obstructive pulmonary disease
CSO	Central Statistics Office
CUA	cost-utility analysis
CV	coverage rate
CVD	cardiovascular diseases
DPS	Drugs Payment Scheme
DRG	Diagnosis Related Group
DSA	deterministic sensitivity analyses
E	latent state
EAG	expert advisory group
ECDC	European Centre for Disease Prevention and Control

ECG	electrocardiography
ED	emergency department
EEA	European Economic Area
EMA	European Medicines Agency
ESRD	end-stage renal disease
ETF	Emergency Task Force
EU	European Union
EUnetHTA	European Network of Health Technology Assessment
EuroMOMO	European mortality monitoring group
FVS	failure susceptible state
GMS	General Medical Service
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	hemagglutinin
HaDEA	Health and Digital Executive Agency
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information And Quality Authority
HPRA	Health Products Regulatory Authority
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
HTA	health technology assessment
I	infectious state
ICU	intensive care unit
ICGP	Irish College of General Practitioners
ICER	incremental cost-effectiveness ratio

IIV	inactivated influenza vaccine
aIIV	adjuvanted inactivated influenza vaccine
ccIIV	cell-based inactivated influenza vaccine
HD-IIV	high dose inactivated influenza vaccine
RIIV	recombinant HA inactivated influenza vaccine
ILI	influenza-like illness
I-MOVE	Influenza - Monitoring Vaccine Effectiveness
JCVI	Joint Committee on Vaccination and Immunisation
LAIV	live attenuated virus vaccines
QLAIV	quadrivalent live attenuated influenza vaccine
LY	life year
LOS	length of stay
LTCF	long-term care facility
MCG	micrograms
MI	myocardial infarction
NA	neuraminidase
NHS	National Health Service
NIAC	National Immunisation Advisory Committee
NIO	National Immunisation Office
NITAG	National Immunisation Technical Group
NMB	net monetary benefits
NRSI	non-randomised studies of intervention
NVRL	National Virus Reference Laboratory
OOH	out-of-hours
OOP	out-of-pocket payment
OR	odds Ratio

OWSA	one-way sensitivity analysis
PICO	Population, Intervention, Comparator and Outcomes
PCR	polymerase chain reaction
PCRS	Primary Care Reimbursement Service
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
PSA	probabilistic sensitivity analyses
QALY	quality-adjusted life year
QIV	quadrivalent influenza vaccine
aQIV	adjuvanted quadrivalent influenza vaccine
ccQIV	cell-based quadrivalent influenza vaccine
HD-QIV	high dose quadrivalent influenza vaccine
R	recovered state
RCT	randomised-controlled trial
RIV4	recombinant quadrivalent influenza vaccine
R_0	reproduction number
RoB	risk of bias
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
RR	relative risk
RSV	respiratory syncytial virus
rVE	relative vaccine effectiveness
S	susceptible
SAE	serious adverse event
SARI	severe acute respiratory infections
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

TIV	trivalent influenza vaccine
aTIV	adjuvanted trivalent influenza vaccine
ccTIV	cell-based trivalent influenza vaccine
HD-TIV	high dose trivalent influenza vaccine
UK	United Kingdom
UKHSA	UK Health Security Agency
URTI	upper respiratory tract infection
US	United States
VAT	value-added tax
VE	vaccine effectiveness
VEBIS	Vaccine Effectiveness, Burden and Impact Studies
VF	vaccine failure
VI	vaccinated infectious state
VR	vaccinated recovered state
VS	vaccinated susceptible state
V1P	vaccinated 1-dose protected state
WHO	World Health Organization
WTP	willingness to pay

1 Introduction

1.1 Background to the request

Seasonal influenza is an acute respiratory infection which places considerable burden on the healthcare system and society in terms of morbidity, mortality, hospitalisations and absenteeism from school and work.[1] The World Health Organization (WHO) estimates that seasonal influenza can affect up to 20% of the population annually, with severe influenza illness accounting for approximately three to five million cases annually, and up to 650,000 respiratory deaths globally.[1] A well-matched, annual influenza vaccination can reduce the risk of getting seasonal influenza. Other preventative measures to complement annual vaccination include personal measures such as avoiding close contact with infected individuals and good hand hygiene.[2]

Annual influenza vaccination programmes internationally aim to reduce the burden of seasonal influenza typically through the selective vaccination of those at highest risk of severe disease.[3] Broadly, influenza vaccines comprise inactivated influenza vaccines (IIVs) made from flu vaccine viruses that have been inactivated (killed), recombinant vaccines which are made using proteins from a flu virus, and live attenuated influenza vaccines (LAIVs) which are made using weakened (attenuated) live flu viruses. The IIVs and recombinant vaccines are administered by intramuscular injection while the LAIVs are administered as an intranasal spray.[4] Trivalent IIVs (or TIVs) are IIVs that contain three strains of influenza virus (two A strains and one B strain), and quadrivalent IIVs (or QIVs) are IIVs that contain four strains of influenza virus (two A strains and two B strains).[5]

Each year, the WHO issues recommendations to vaccine manufacturers relating to vaccine content and the specific viral subtyping that should be contained within.[6] In the Northern Hemisphere, these recommendations are typically published in February to inform the upcoming influenza season (that is, October the same year to May the following year). These recommendations are based on global surveillance data and are critical to the effectiveness of influenza vaccines.[7] However, due to the continuous evolution of the influenza virus, antigenic mismatch between the virus strains contained in the vaccine and those in circulation can occur. Strain mutation can also occur during traditional vaccine manufacture that relies on egg-based vaccine production processes. These issues can contribute to reduced vaccine effectiveness.[8] Another factor affecting vaccine effectiveness is the individual's immune response, which can be suboptimal due to an ageing or compromised immune system — for example, in older adults (aged 65 years and older) or those with an immunocompromising condition.[9] As such, enhanced IIVs have been developed in an attempt to increase vaccine effectiveness. These include:

- adjuvanted IIV (aIIV) — IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response
- high-dose IIV (HD-IIV) — IIV which contains a four-fold increase of haemagglutinin (HA) per strain (that is, 60µg) instead of 15µg of HA typically included in a standard dose IIV[10]
- vaccines manufactured using alternative substrates to the traditional egg-derived processes, thereby removing the possibility of strain mutation associated with egg-based propagation:
    - cell-based IIV (ccIIV) — IIV manufactured using mammalian cell-culture
    - recombinant HA IV (RIIV) — IIV manufactured using recombinant HA proteins.[10]

In Ireland, guidance from the National Immunisation Advisory Committee (NIAC) recommends an adjuvanted QIV (aQIV) for those aged 65 years and older;[11] a standard QIV is recommended if an aQIV is not available. Currently, only standard QIVs are reimbursed for this age group as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme.[12] In order to inform a decision as to whether enhanced IIVs should be reimbursed as part of the HSE Seasonal Influenza Vaccination Programme, the Department of Health requested that HIQA complete a health technology assessment (HTA) of universal vaccination with an enhanced IIV in those aged 65 years and older.

1.2 Terms of reference

The HTA will be submitted as advice to the Minister for Health and HSE to inform a decision on universal vaccination with an enhanced IIV in those aged 65 years and older. 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.

With consideration to the population aged 65 years and older, the terms of reference for this HTA, agreed with the Department of Health, were to:

- describe the enhanced inactivated influenza vaccines (IIVs) authorised for use
- conduct a review of the use of enhanced IIVs in immunisation programmes in EU/EEA countries and the UK

- describe the epidemiology and burden of disease associated with influenza in Ireland
- review the current evidence of the clinical effectiveness and safety of enhanced IIVs
- review the methodology for economic modelling studies of IIVs
- assess the cost effectiveness and budget impact of universal vaccination in Ireland with an enhanced IIV
- consider any potential organisational and resource implications of universal vaccination with an enhanced IIV
- consider any ethical, patient and social implications that universal vaccination with an enhanced IIV may have for patients, the general public and the healthcare system in Ireland
- based on the findings of this assessment, provide advice to inform a decision on universal vaccination with an enhanced IIV in those aged 65 years and older.

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 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 Department of Health

- 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 its first meeting. The protocol and draft chapters on the description of the technology, epidemiology and burden of disease and the review of economic modelling studies were circulated to the EAG and also discussed at that meeting. Following incorporation of feedback from the EAG, these draft chapters along with draft chapters on the remaining HTA domains (that is, clinical effectiveness and safety, cost effectiveness, budget impact analysis, organisational issues, ethical, patient and social considerations) were circulated to the EAG in advance of the second EAG meeting and discussed at that meeting. Following incorporation of further feedback from the EAG at its second meeting, a draft version of the completed report was circulated for review by the EAG and amended, as appropriate, before a final draft report was prepared for public consultation. After the public consultation, a final draft version of the report and the advice to the Minister for Health and HSE were circulated for review by the EAG. The report was then submitted to the Board of HIQA for approval. Following its approval, the completed assessment was submitted to the Minister for Health and HSE as advice, and published on the HIQA website.

2 Description of the technology

Key points

- Annual vaccination is an important preventive measure to reduce the burden associated with seasonal influenza. Vaccine schedules internationally aim to reduce the burden of seasonal influenza, typically through the selective vaccination of those at highest risk of severe disease.
- Available inactivated influenza vaccines (IIVs) include standard trivalent IIVs (TIVs), standard quadrivalent IIVs (QIVs) and enhanced IIVs; enhanced IIVs were developed to improve vaccine effectiveness. These enhanced IIVs include:
    - adjuvanted IIV (aIIV) — IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response
    - high-dose IIV (HD-IIV) — IIV which contains a four-fold increase of HA per strain (that is, 60µg) instead of 15µg of HA typically included in a standard dose IIV
    - vaccines manufactured using alternative substrates to the traditional egg-derived processes, thereby removing the possibility of strain mutation associated with egg-based propagation:
        - cell-based IIV (ccIIV) — IIV manufactured using mammalian cell-culture
        - recombinant HA IV (RIIV) — IIV manufactured using recombinant HA proteins.
- Three standard QIVs have been nationally authorised through the Health Products Regulatory Authority (HPRA), of which two were funded as part of the 2023-2024 HSE Seasonal Influenza Vaccination Programme.
- As of April 2024, three enhanced IIVs have been centrally authorised through the European Medicines Agency (EMA) and one enhanced IIV (HD-QIV) has been nationally authorised through the HPRA; none are marketed in Ireland.
- Ireland's National Immunisation Advisory Committee (NIAC) recommends an adjuvanted QIV (aQIV) for those aged 65 years and older, or a standard QIV if an aQIV is not available. Currently, no enhanced IIV is funded through the HSE Seasonal Influenza Vaccination Programme.
- Data on influenza vaccination programmes and funding of the same, for

EU/EEA countries, were extracted from the European Centre for Disease Prevention and Control (ECDC) Vaccine Scheduler. Influenza vaccine policies for each EU/EEA country and the UK were also individually reviewed to reflect the most recently available information regarding vaccine type (that is, standard or enhanced) and funding status.

- All EU/EEA countries and the UK recommend influenza vaccination for those aged 65 years and older although countries differ with regard to their funding policies and the vaccine types used. For the 2023-2024 influenza season:
    - Considering the target population, 24 of 31 countries fully fund influenza vaccinations, three countries partly fund influenza vaccinations, three countries do not fund influenza vaccinations, and funding in one country varies by region.
    - Ten of 31 countries fund an enhanced IIV for some or all of the target population. Six of these specifically fund a HD-QIV; one funds an aQIV; one funds an aQIV, HD-QIV or ccQIV; one funds an aQIV, RIV4 or ccQIV; and one funds all four enhanced IIVs (aQIV, HD-QIV, RIV4 or ccQIV).
    - Five countries (Belgium, Liechtenstein, Norway, Portugal and Sweden) restrict availability to subgroups of the target population — for example, to those aged 75 years and older, or those living in long-term care facilities. Three of these countries (Belgium, Liechtenstein and Portugal) fund enhanced IIVs, one country (Norway) does not, and in one country (Sweden), funding varies by region.

2.1 Introduction

The purpose of this chapter is to describe the enhanced inactivated influenza vaccines (IIVs) currently authorised in Ireland that serve as a tool to prevent influenza A and B virus infection causing seasonal influenza. This chapter also provides background on influenza's potential as a pathogen and the resulting disease. These will be explored in greater detail in Chapter 3. A description of the current Health Service Executive (HSE) Seasonal Influenza Vaccination Programme for those aged 65 years and older is described. Lastly, a description of influenza vaccination programmes currently in place in the EU and UK for those aged 65 years and older is provided.

2.2 Pathogen

Influenza viruses are RNA viruses from the Orthomyxoviridae family.[13] They circulate primarily through droplet transmission, aerosol transmission and contact transmission.[14] There are four types of influenza viruses — type A, B, C and D. Influenza A and B circulate globally, typically from November to April in the Northern Hemisphere, and from June to October in the Southern Hemisphere.[15] Influenza C is less common and responsible for only mild infections, while influenza D is predominantly found in cattle. Influenza A viruses are categorised into subtypes, according to the combination of glycoproteins (haemagglutinin (HA) and neuraminidase (NA)) present on the surface of the virus.[16] Influenza B viruses do not have sub-types, but instead have two antigenically distinct lineages, Victoria and Yamagata.[15]

In humans, influenza viruses preferentially bind to cell surface receptors called sialyloligosaccharides which are mainly found in the upper and lower respiratory tract. Influenza viruses enter (via inhalation and direct or indirect contact) and exit (via coughing, sneezing and talking) the host through the mouth and nose.[14] Influenza has an incubation period of approximately two days (range 1-4 days), and can be transmitted 24 hours before the onset of clinical symptoms and up to five days (or up to seven days in children) after disease onset.[17]

Influenza viruses are an example of specific viral infections that may induce a process known as original antigenic sin (OAS). The OAS concept, first proposed in 1960, suggests that the first variant of an influenza virus encountered early in life will dictate lifelong immunity to all subsequently encountered antigenic variants of that virus.[18, 19] According to this concept, the initial viral infection will establish an immunological fingerprint that specifically imprints on the immune system in response to that virus. Second or subsequent exposure to a different antigenic strain of the same influenza virus will result in an immune response with antibodies of less strength and specificity to this variant strain. While the applicability of this concept to influenza viruses has been challenged in the literature, what is known is that immune memory acquired by past influenza exposure influences the response to subsequent strains.[19] Whether, or the extent to which, this previous exposure negatively impacts immune responses to subsequent infections by antigenic variants is not known for influenza. Modern vaccine strategies aim to mitigate the potential effects of OAS, including but not limited to the use of adjuvants, higher doses of HA antigen and vaccines manufactured using mammalian cell-culture or recombinant technology to remove the possibility of strain-mutation associated with traditional egg-based technology.[10, 18]

2.3 Disease

The focus of this assessment is seasonal influenza rather than pandemic influenza. Seasonal influenza circulation occurs annually due to subtle changes in existing HA and NA glycoproteins, but this process results in no change in the influenza A subtype. On the other hand, influenza pandemics are the result of major changes in surface HA and NA glycoproteins which generate a new influenza A virus and subtype. There have been four such pandemics within the last century (with an inter-pandemic interval range of 11 years to 39 years); the last influenza pandemic was in 2009.[20]

As discussed, influenza A and B are the main focus in the context of seasonal influenza. Currently, there are 18 HA (H1-H18) and 11 NA (N1-N11) subtypes, with influenza A(H1N1) and A(H3N2) most commonly circulating. The influenza B viruses fall into two major lineages (B/Victoria and B/Yamagata).[16] Seasonal influenza A and B viruses are able to escape human humoral immunity by initiating changes in the coding for glycoproteins (HA and NA). This process is known as antigenic drift and it drives annual seasonal influenza cases.[21] Seasonal influenza places considerable burden on the healthcare system and society in terms of morbidity, mortality, hospitalisations and absenteeism from school and work. The World Health Organization (WHO) estimates that globally, seasonal influenza can affect up to 20% of the population, with severe influenza illness accounting for approximately three to five million cases annually, and up to 650,000 respiratory deaths.[1]

Seasonal influenza is characterised by respiratory and systemic symptoms including cough, shortness of breath, fever, malaise, myalgia, headache, sore throat and nasal congestion. Gastrointestinal symptoms such as nausea, vomiting and diarrhoea are also common. The range and severity of symptoms vary substantially across infected individuals. In most healthy individuals, seasonal influenza is self-limiting and symptoms typically resolve in three to seven days. Treatment for these individuals consists of antipyretics, adequate fluid intake and rest. However, certain individuals have an increased risk of severe disease and may require hospitalisation.[22] Those at elevated risk of severe disease include those with underlying medical conditions (such as chronic respiratory disease, chronic heart disease and diabetes), infants and young children, pregnant women and those aged 65 years and older.[23]

Influenza is associated with a range of respiratory and non-respiratory complications. Otitis media, parotitis, sinusitis and laryngotracheobronchitis are all upper respiratory complications, and, with the exception of sinusitis, all are more common in children than in adults. Lower respiratory complications include bronchiolitis (which is more common in young children than adults), bronchitis, pneumonia, respiratory failure and acute respiratory distress syndrome.[21]

Non-respiratory complications include:

- cardiac complications (such as myocardial infarction, myocarditis, pericarditis and heart failure)
- gastrointestinal complications (such as hepatitis and pancreatitis)
- renal complications (such as acute kidney injury and kidney failure)
- neurological complications (such as encephalopathy, encephalitis, meningoencephalitis and febrile seizures)
- general complications (such as exacerbation of chronic disease, dehydration and sepsis).[21]

Additionally, patients infected with influenza can experience co-infection with other pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV) and others, which can contribute to increased morbidity and mortality. In a population study conducted in England, it was reported that, after adjusting for age, sex, ethnicity, comorbidity and co-infection status, those with a SARS-CoV-2 and influenza co-infection were around twice as likely to die (odds ratio (OR) 2.27, 95% confidence interval (CI): 1.23–4.19) compared with those with SARS-CoV-2 infection only.[24]

2.4 Vaccines

This section is limited to influenza vaccines currently authorised in the EU for the population under review, that is, adults aged 65 years and older.

2.4.1 Vaccine description

In the mid-1930s, the first clinical trials of an IIV, which was active against the H1N1 strain of influenza A, were undertaken. Subsequently, in 1945, the first IIV was licensed in the US. In the meantime, a new strain of influenza, type B, was identified, and in 1942, an inactivated bivalent influenza vaccine, active against both influenza type A and type B, was tested.[25] As new influenza strains have continued to emerge (as a result of the mutation of surface glycoproteins), scientists have continued to develop IIVs that are active against an increased number of influenza strains. These have included trivalent IIVs (TIVs) which comprise two influenza A antigens (A(H1N1)pdm09 and A(H3N2)) and one influenza B antigen (either the B/Victoria or B/Yamagata lineage depending on which was expected to contribute most to annual influenza burden in the next season), and quadrivalent IIVs (QIVs) which comprise antigens of both the B/Victoria and B/Yamagata lineages in addition to the two influenza A antigens.[26]

Influenza vaccines are most effective when they are strain-specific, that is, they match the influenza strain currently circulating. However, as described previously,

antigenic drift enables influenza viruses to escape immunity. To facilitate strain-specific vaccination, the WHO established the Global Influenza Network in 1952.[27] This network consists of a number of collaborative centres around the world who are responsible for monitoring antigenic drift and emerging virus strains. Using global surveillance data, the WHO issues annual recommendations to vaccine manufacturers regarding vaccine strain inclusion.[10]

In March 2024, the European Medicines Agency (EMA) Emergency Task Force (ETF) issued a recommendation regarding the replacement of QIVs with TIVs in the EU. This Task Force recommendation was on the foot of the February 2024 update report from the WHO which outlined its recommendations to manufacturers for influenza vaccine composition for the 2024-2025 Northern Hemisphere influenza season. Specifically, the WHO recommended the removal of antigens for the B/Yamagata lineage from seasonal influenza vaccines. Reports from the EMA and WHO highlighted that there has been no confirmed detection of the naturally occurring B/Yamagata virus since March 2020 and, as such, the relevance of vaccinating against this lineage has been questioned. Moreover, the reports highlighted the potential that live attenuated virus vaccines (LAIVs) containing the B/Yamagata antigen could pose a risk of the lineage being reintroduced into humans.

This recommendation would mean a move back from quadrivalent to trivalent and applies to both IIVs and LAIVs. The EMA's report recognises that in the EU/EEA, the use of quadrivalent vaccines has completely replaced the use of trivalent vaccines, with only a small number of trivalent vaccine marketing authorisations still valid in EU Member States in 2024. Given this, the ETF has recommended a well-planned transition from quadrivalents to trivalents, with continuous monitoring to confirm the disappearance of B/Yamagata. The ETF recommended starting the process of re-authorising trivalent vaccines by prioritising trivalent LAIVs for which there could be a potential risk of the reintroduction of B/Yamagata, followed by the re-authorisation of trivalent IIVs. They have recommended that, ideally, the antigens of the B/Yamagata lineage should be removed from LAIVs for the 2024-2025 influenza season. For IIVs (which are the subject of this HTA), they have recommended that the B/Yamagata lineage should be removed for the 2025-2026 season as there is no public health concern requiring an immediate transition, and vaccine availability is of primary importance.[28]

As noted above, global surveillance data are used to inform annual WHO recommendations to vaccine manufacturers regarding vaccine strain inclusion. While strain-specific vaccines are a key component of vaccine effectiveness, the immune response produced can still be suboptimal. This may be due to an ageing or compromised immune system, for example, in older adults (those aged 65 years and

older) or those with an immunocompromising condition.[9] As such, enhanced IIVs have been developed in an attempt to increase vaccine effectiveness, including:

- adjuvanted IIV (aIIV) — IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response compared with standard IIVs
- high-dose IIV (HD-IIV) — IIV which contains a four-fold increase of HA per strain (that is, 60µg, instead of 15µg of HA typically included in a standard IIV dose) to produce an enhanced immunological response compared with standard IIVs
- vaccines manufactured using alternative substrates to the traditional egg-derived processes, thereby removing the possibility of strain mutation associated with egg-based propagation:[10]
    - cell-based IIV (ccIIV) — IIV manufactured using mammalian cell culture
    - recombinant HA IV (RIIV) — IIV manufactured using recombinant HA proteins.[29] The RIIV contains a threefold increase of HA per strain (45µg versus 15µg of HA typically included in a standard IIV dose). While technically also a higher dose vaccine, this vaccine will be referred to in this HTA as RIIV to distinguish it from the HD-IIV which contains 60µg of HA per strain.

In Ireland, the National Immunisation Advisory Committee (NIAC) recommends an aQIV for the target population (those aged 65 years and older) and a standard QIV if an aQIV is not available. Currently, only standard QIVs are available and funded through the HSE Seasonal Influenza Vaccination Programme.[30]

The EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines across the EU. Vaccines may be centrally authorised through the EMA or alternatively they may be nationally authorised in individual member states by the national competent authorities. In Ireland, the Health Products Regulatory Authority (HPRA) is the national competent authority for medicines.

Considering the enhanced IIVs that are the target of this HTA, three have been centrally authorised through the EMA and a fourth has been nationally authorised by the HPRA; see Table 2.1. Flucelvax Tetra®, which is a cell-based QIV (ccQIV) for adults and children aged two years and older (manufactured by Seqirus Netherlands B.V.), was authorised by the EMA in December 2018.[31] Fluad Tetra®, which is an aQIV for adults aged 65 years and older (also manufactured by Seqirus Netherlands B.V.), was authorised by the EMA in May 2020.[32] Supemtek®, which is a

recombinant HA quadrivalent influenza vaccine (RIV4) for use in adults aged 18 years and older (manufactured by Sanofi), was authorised by the EMA in November 2020.[33] As of September 2023, no HD-IIV has been centrally authorised by the EMA. However, Efluelda® (a high-dose QIV (HD-QIV) manufactured by Sanofi) was authorised by the HPRA in Ireland in April 2020.[34]

While all medicines are monitored after EU market authorisation has been granted, some medicines are monitored more closely than others.[35] The EMA publishes a list of medicines for which additional monitoring is required,[36] which is reviewed monthly by the Pharmacovigilance Risk Assessment Committee (PRAC).[35] This list specifies the reason for which additional monitoring is required,[36] and medicines which are published on this list are distinguished by a black inverted triangle and accompanying warning displayed on both product SmPC and package leaflet.[37] Additional monitoring aims to enhance reporting of suspected adverse drug reactions for medicines for which the clinical evidence base is less well developed. It therefore always applies in the case of medicines that contain either a new active substance, or where the medicine is a new biological medicine (for example, a vaccine). Fluad Tetra®, Supemtek®, Efluelda®, Quadrivalent Influenza Vaccine are on the EMA's list of medicines requiring additional monitoring.[36] Medicines may remain under additional monitoring for five years, or until the PRAC decides to remove them from the list.

A summary of the key characteristics of the enhanced IIVs and a summary of the key characteristics of the standard IIVs are provided in Table 2.1 and Table 2.2, respectively.

2.4.2 Co-administration with other vaccines

All of the influenza vaccines described above are available as pre-filled syringes and can be given at the same time as other vaccines; the incidence of adverse events may be higher compared to when these vaccines are administered alone. Guidance from NIAC regarding injection sites should be followed.[11]

On 21 October 2021, the WHO recommended that countries can consider the co-administration of influenza vaccines and COVID-19 vaccines during the same visit. This reduces the number of clinic visits for the individual and decreases the overall burden at a health systems level.[38] The WHO noted that while there may be an increased risk of adverse events associated with this co-administration, the limited evidence available did not indicate an increased level of adverse reactions. In Ireland, in accordance with advice from the NIAC, COVID-19, seasonal influenza and 23-valent pneumococcal polysaccharide PPV23 vaccines can be co-administered.[30]

In February 2024, the UK Health Security Agency (UKHSA) presented data from studies investigating the effect of co-administration of respiratory syncytial virus (RSV) vaccines and IIVs in older adults at a Joint Committee of Vaccination and Immunisation (JCVI) meeting in the UK.[39] The data presented pertained to a number of studies where IIVs (specifically standard QIV, HD-IIV or aQIV) were co-administered with RSV vaccines (including Abrysvo® (manufactured by Pfizer), Arexvy® (manufactured by GlaxoSmithKline), and mRNA-1345 (manufactured by Moderna, not currently licensed)). While a summary of the data was presented, only one study appears to be published at the time of the JCVI meeting, which investigated the co-administration of Abrysvo® and aQIV.[40] Overall, the UKHSA found that, while there were no reactogenicity concerns with co-administration of RSV and IIVs (high confidence), there were potential reductions in immunogenicity. As such, until more follow-up data become available, the UKHSA recommend that it may be preferable to avoid co-administration where possible for older adults. However, co-administration is not contra-indicated, and may be considered where it is deemed likely that an individual may not attend a second scheduled appointment.[39] In keeping with this, NIAC also recommend the co-administration of seasonal influenza and COVID-19 vaccines where practicable to maximise uptake.[11]

2.4.3 Administration and manufacturers stipulated storage

The manufacturers' instructions for Flucelvax Tetra®,[31] Fluad Tetra®,[32] Supemtek® and Fluarix Tetra® state that they should be administered by intramuscular injection only.[33, 41] The manufacturers' instructions for Quadrivalent Influenza Vaccine, Influvac Tetra® and Efluelda® state that they should be administered by intramuscular or deep subcutaneous injection.[34, 42, 43] The preferred sites for intramuscular injection for adults is the deltoid muscle.

All seven vaccines (standard and enhanced) should be stored in a refrigerator at 2°C to 8°C.[31-34, 41-43] They should not be frozen, and the syringe should be kept in the outer packaging to protect it from light. All should be allowed to reach room temperature before use and should be visually inspected for particulate matter and discolouration prior to administration. All seven vaccines should be gently shaken before administration.

2.4.4 Dosing schedule

For six vaccines (Flucelvax Tetra®, Fluad Tetra®, Supemtek®, Fluarix Tetra®, Quadrivalent Influenza Vaccine and Influvac Tetra®) the dose for adults is 0.5ml;[31-33, 41-43] the dose for Efluelda® is 0.7ml.[34] It should be noted that all seven IIVs described in this HTA (as seen in Table 2.1 and Table 2.2) are QIV formulations. Given the recommendation issued by the WHO in February 2024, advising the removal of antigens for the B/Yamagata lineage from seasonal influenza vaccines, it

is expected that these formulations will be updated to TIV formulations for future seasons.[6] Annual influenza vaccination is recommended given the duration of immunity provided by the vaccine and because circulating strains of influenza virus change from year to year.

Table 2.1 Summary of key characteristics of authorised enhanced inactivated influenza vaccines

Trade name	Flucelvax Tetra®[31]	Fluad Tetra®[32]	Supemtek®[33]	Efluelda®[34]
Vaccine type	Cell-based quadrivalent influenza vaccine	Adjuvanted quadrivalent influenza vaccine	Recombinant HA quadrivalent influenza vaccine	High-dose quadrivalent influenza vaccine
Manufacturer	Seqirus Netherlands B.V.	Seqirus Netherlands B.V.	Sanofi	Sanofi
License issued	12 December 2018	20 May 2020	16 November 2020	24 April 2020
Marketing status	Unknown	Unknown	Unknown	Not marketed
Formulation	Per 0.5ml dose, influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains*: ▪ A/XXXXXX (H1N1) 15 mcg HA ▪ A/XXXXXX (H3N2) 15 mcg HA ▪ B/XXXXXX 15 mcg HA ▪ B/XXXXXX 15 mcg HA *propagated in Madin Darby Canine Kidney (MDCK) cells.	Per 0.5ml dose, influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains*: ▪ A/XXXXXX (H1N1)15 mcg HA ▪ A/XXXXXX (H3N2) 15 mcg HA ▪ B/XXXXXX 15 mcg HA ▪ B/XXXXXX 15 mcg HA *propagated in fertilised hens' eggs from healthy chicken flocks and adjuvanted with MF59C.1	Per 0.5 ml dose, influenza virus haemagglutinin proteins, of the following strains*: ▪ A/XXXXXX (H1N1) 45 mcg HA ▪ A/XXXXXX (H3N2) 45 mcg HA ▪ B/XXXXXX 45 mcg HA ▪ B/XXXXXX 45 mcg HA *produced by recombinant DNA technology using a baculovirus expression system in a continuous insect cell line that is derived from Sf9 cells of the fall armyworm, Spodoptera frugiperda.	Per 0.7ml dose, influenza virus (inactivated, split) of the following strains*: ▪ A/XXXXXX (H1N1) 60 mcg HA ▪ A/XXXXXX (H3N2) 60 mcg HA ▪ B/XXXXXX 60 mcg HA ▪ B/XXXXXX 60 mcg HA *propagated in embryonated chicken eggs.
Therapeutic indications	▪ Prophylaxis of influenza in adults and children from 2 years of age. ▪ Flucelvax Tetra® should be used in accordance with official recommendations.	▪ Prophylaxis of influenza in older people (65 years of age and older). ▪ Fluad Tetra® should be used in accordance with official recommendations.	▪ Active immunisation for the prevention of influenza in adults. ▪ Supemtek® should be used in accordance with official recommendations.	▪ Active immunisation in adults ≥60 years for prevention of influenza. ▪ The use of Efluelda® should be based in accordance with official recommendations.
Subject to additional monitoring requirements by the EMA	No.	Yes, Fluad Tetra® has been subject to additional monitoring since June 2020 owing to the fact that it is a new biological medicine.[36]	Yes, Supemtek® has been subject to additional monitoring since November 2020 owing to the fact that it is a new biological medicine.[36]	Yes, Efluelda® has been subject to additional monitoring since February 2021 owing to the fact that it is a new biological medicine.[36]

Key: EU – European Union; HA – haemagglutinin; mcg – micrograms.

Note: The composition of these vaccines comply with the annual EMA-issued EU recommendations, which are made on the basis of observations by the WHO (Northern Hemisphere), for the respective influenza season.

Table 2.2 Summary of key characteristics of authorised standard inactivated influenza vaccines

Trade name	Quadrivalent Influenza Vaccine®[42]	Influvac tetra®[43]	Fluarix tetra®[41]
Vaccine type	Quadrivalent influenza vaccine	Quadrivalent influenza vaccine	Quadrivalent influenza vaccine
Manufacturer	Sanofi	Viatris Healthcare Limited	GlaxoSmithKline (Ireland) Limited
License issued	15 July 2016	25 August 2017	1 June 2018
Marketing status	Marketed	Marketed	Not marketed
Formulation	Per 0.5ml dose, influenza virus (inactivated, split) of the following strains*: ▪ A/XXXXXX (H1N1) 15 mcg HA ▪ A/XXXXXX (H3N2) 15 mcg HA ▪ B/XXXXXX 15 mcg HA ▪ B/XXXXXX 15 mcg HA *propagated in fertilised hens' eggs from healthy chicken flocks.	Per 0.5ml dose, influenza virus surface antigens, inactivated, (haemagglutinin and neuraminidase) of the following strains*: ▪ A/XXXXXX (H1N1) ▪ A/XXXXXX (H3N2) 15 mcg HA ▪ B/XXXXXX 15 mcg HA ▪ B/XXXXXX 15 mcg HA *propagated in fertilised hens' eggs from healthy chicken flocks.	Per 0.5ml dose, influenza virus (inactivated, split) of the following strains*: ▪ A/XXXXXX (H1N1) 15 mcg HA ▪ A/XXXXXX (H3N2) 15 mcg HA ▪ B/XXXXXX 15 mcg HA ▪ B/XXXXXX 15 mcg HA *propagated in fertilised hens' eggs from healthy chicken flocks.
Therapeutic indications	Prevention of influenza for: ▪ active immunisation of adults, including pregnant women, and children from 6 months of age and older ▪ passive protection of infant(s) from birth to less than 6 months of age following vaccination of pregnant women. Use of Quadrivalent Influenza Vaccine should be based on official recommendations.	Prophylaxis of influenza, especially those who run an increased risk of associated complications. Influvac Tetra® is indicated in adults and children from 6 months of age. The use of Influvac Tetra® should be based on official recommendations.	Active immunisation of adults and children from 6 months of age for the prevention of influenza disease. Use of Fluarix Tetra® should be based on official recommendations. Annual revaccination is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus might change from year to year.
Subject to additional monitoring requirements by the EMA	Yes, Quadrivalent influenza vaccine has been subject to additional monitoring since January 2020 owing to the fact that it is a new biological medicine.[36]	No.	No.

Key: HA – haemagglutinin; mcg – micrograms.

Note: The composition of these vaccines comply with the annual EMA-issued EU recommendations, which are made on the basis of observations by the WHO (Northern Hemisphere), for the respective influenza season.

2.5 Current influenza vaccination schedules

Vaccination schedules internationally aim to reduce the burden of seasonal influenza typically through the selective vaccination of those at highest risk of severe disease. In Ireland, for the 2023-2024 influenza season, all vaccines funded for adults through the HSE Seasonal Influenza Vaccination Programme were standard QIVs.[44]

In Europe, all EU/EEA countries manage their own national public health policy, which includes an immunisation programme.[45] Data on influenza vaccination programmes and funding of the same, for EU/EEA countries, were extracted from the European Centre for Disease Prevention and Control (ECDC) Vaccine Scheduler.[46] The scheduler reflects recommendations up to the 2023-2024 season and may be subject to change. Influenza vaccine policies for each EU/EEA country and the UK were also individually reviewed to reflect the most recently available information regarding vaccine type (that is, standard or enhanced) and funding status; see Table 2.3. The following information is accurate as of 8 April 2024.

All EU/EEA countries and the UK have influenza vaccination programmes which include those aged 65 years and older, although countries differ in the vaccine types offered and funded:

Standard influenza vaccines

- Countries which offer and fund (in full) standard IIVs for the target population are: Croatia (standard QIV), Cyprus (standard TIV), Czech Republic (standard QIV), Denmark (standard QIV), Estonia (standard IIV), Finland (standard QIV), Hungary (standard TIV), Iceland (standard QIV), Ireland (standard QIV), Lithuania (standard TIV), Luxembourg (standard QIV), Malta (standard TIV), Netherlands (standard QIV), Poland (standard QIV), Slovakia (standard QIV), Slovenia (standard QIV) and Spain (standard QIV).
- Countries which offer but do not fund standard IIVs for the target population are: Bulgaria (standard IIV) and Romania (standard QIV).

Enhanced influenza vaccines

- Countries which offer and fund (in full) enhanced IIVs for the target population are: France (HD-QIV), Latvia (HD-QIV) and the UK (aQIV, RIV4 or ccQIV).
- Austria offers and funds (in part) an enhanced IIV for the target population (aQIV).

Combination of standard and enhanced influenza vaccines

Several countries offer a combination of standard IIVs and enhanced IIVs for the target population, but the availability of enhanced IIVs may be restricted to specific subgroups (for example, to those aged 75 years and older or living in residential care).

- Countries which offer and fund (in full) standard and or enhanced IIVs for the target population are: Germany (standard QIV or HD-QIV), Greece (aQIV or HD-QIV, also ccQIV or standard QIV), Italy (aQIV or HD-QIV, also standard QIV, RIV4 or ccQIV) and Portugal (standard QIV or HD-QIV).
- Countries which offer and fund (in part) standard and or enhanced IIVs for the target population are: Belgium (standard QIV or HD-QIV) and Liechtenstein (standard QIV or HD-QIV).
- Norway offers standard and or enhanced IIVs (standard QIV or aQIV) for the target population, but these are not funded for those aged 65 years and older specifically. Healthcare workers with patient contact; laboratory personnel who handle samples that may contain influenza viruses; people who work with live pigs; and sanitation workers and other personnel who are exposed to domesticated birds with suspected or confirmed avian influenza as part of their job are reimbursed any vaccination costs by their employer.
- Funding of influenza vaccinations for the target population varies by region in Sweden (standard QIV or aQIV).

See Table 2.3 for an overview of national-level influenza vaccination programmes in EU/EEA countries and UK for those aged 65 years and older.

Of note, countries may also differ as to when they start their national-level vaccination programmes; start times may be influenced by when influenza notifications or hospitalisations typically peak in the country. For example, the JCVI in the UK have advised moving the start of their Seasonal Influenza Vaccination Programme for most adults to the beginning of October, given the evidence that the effectiveness of the IIVs can wane over time in adults. By starting the programme in October, the majority of people should be vaccinated by the end of November, which is closer to the time that influenza peaks in the UK (typically December or January); this provides optimal protection during the highest risk period.[47]

Table 2.3 Overview of national-level influenza vaccination programmes in EU/EEA countries and UK for the target population, as of 8 April 2024

Country	Season	Vaccine type offered	Funding information
Austria	2023-2024	aQIV for those aged 65 years and older.[48, 49]	From October 2023 vaccination is offered to all people living in Austria with a seven euro deductible per vaccination, regardless of age or insurance status.[48, 49] Vaccination is free to a number of groups including people living in nursing homes.[49, 50]
Belgium	2023-2024	Standard QIV for those aged 65 years and older.[51, 52] HD-QIV for those aged 65 years and older and staying in a residential care establishment or other type of institution.[51, 52]	Partial funding for standard QIV.[52] HD-QIV only funded for those aged 65 years and older and staying in a residential care establishment or other type of institution.[51, 52]
Bulgaria	2023-2024	*Standard IIV (no specification as to whether TIV or QIV are used).[46]	*Vaccination not funded as part of national immunisation programme.[46]
Croatia	2023-2024	Standard QIV[53]	Vaccination is free of charge as part of national immunisation programme for a number of groups including people aged 65 years and older.
Cyprus	2023-2024	*Standard TIV[54] ref	*Vaccination funded as part of national immunisation programme.[46]
Czech Republic	2023-2024	*Standard QIV[46]	*Vaccination funded as part of national immunisation programme for those aged 65 years and older.[46]
Denmark	2023-2024	Standard QIV[55, 56] ref	Vaccination funded as part of national immunisation programme for those aged 65 years and older.[55, 57]
Estonia	2023-2024	*Standard IIV (no specification as to whether TIV or QIV are used).[46]	Vaccination funded as part of national immunisation programme for those aged 60 years and older.[58]
Finland	2023-2024	Standard QIV[59]	Vaccination funded by national immunisation programme for those aged 65 years and older.[59]
France	2023-2024	HD-QIV[60]	Vaccination funded for those aged 65 years and older by national health insurance (which is compulsory in France).[60]

Country	Season	Vaccine type offered	Funding information
Germany	2023-2024	HD-QIV for those aged 60 years and older. Standard QIV can be administered if HD-QIV not available.[61]	Vaccination funded by national immunisation programme for those aged 60 years and older.[62, 63]
Greece	2023-2024	HD-QIV or aQIV for those aged 65 years and older; ccQIV or standard QIV can be administered if these are not available.	Vaccination funded by national immunisation programme for those aged 60 years and older.[64]
Hungary	2023-2024	*Standard TIV[46]	*Vaccination funded by national immunisation programme for those aged 60 years and older.[46]
Iceland	2023-2024	*Standard QIV[46, 65]	Vaccination funded by national immunisation programme for those aged 60 years and older.[66]
Ireland	2023-2024	Standard QIV[23]	Vaccination funded by national immunisation programme for those aged 65 years and older.[23]
Italy	2023-2024	aQIV or HD-QIV recommended for those aged 65 years and older. Standard QIV, RIV4 and ccQIV can be administered if aQIV or HD-QIV is not available.[67, 68]	Vaccination funded as part of national immunisation programme for those aged 60 years and older.[67]
Latvia	2023-2024	HD-QIV[69]	Vaccination funded by national immunisation programme for those aged 65 years and older.[70]
Liechtenstein	2024-2025	Standard QIV or HD-QIV for all those 65 years and older.[71]	Full funding of Standard QIV for all those 65 years and older.[71] Full funding of HD-QIV for those aged 75 years and older as well as those aged 65 years and older with at least one other risk factor.[71]
Lithuania	2023-2024	*Standard TIV[72]	*Vaccination funded as part of national immunisation programme.[72]
Luxembourg	2023-2024	*Standard QIV[73]	Vaccinations funded by the National Health Insurance Fund for those aged 65 years and older.[73]
Malta	2023-2024	*Standard TIV[74]	*Vaccination funded by national immunisation programme for those aged 55 years and older.[74]

Country	Season	Vaccine type offered	Funding information
Netherlands	2022-2023	Standard QIV[75]	Vaccination funded by national immunisation programme for those aged 60 years and older.[75, 76]
Norway	2023-2024	Standard QIV[77] aQIV is available to residents in nursing homes and people on the waiting list for such housing.[77]	Vaccination not funded as part of national immunisation programme.[78]
Poland	2023-2024	Standard QIV[79]	Vaccination funded as part of national immunisation programme for those aged 65 years and older.[79]
Portugal	2023-2024	Standard QIV[80] HD-QIV available for those in residential facilities for older people.[80]	Full reimbursement of standard QIV for all those aged 60 years and older. Full funding of HD-QIV for those in residential facilities for older people.[80, 81]
Romania	2022-2023	Standard QIV[82]	*Vaccination not funded as part of national immunisation programme.[82]
Slovakia	2022-2023	Standard QIV[83]	*Vaccination funded as part of national immunisation programme.[83]
Slovenia	2023-2024	Standard QIV[84]	Influenza vaccination is free of charge for all people with mandatory health insurance.[84]
Spain	2023-2024	Standard QIV[85]	*Vaccination funded as part of national immunisation programme.[85-88]
Sweden	2023-2024	Standard QIV[89] aQIV offered primarily to those 65 years and older living in nursing homes.[89]	Vaccination funding varies by region.[89]
UK	2024-2025	aQIV or RIV4 for those 65 years and older. If not available use ccQIV.[90]	Vaccination funded as part of national immunisation programme. This did not represent a change from the 2023-2024 season.[91]

Key: aQIV – adjuvanted quadrivalent influenza vaccine; ccQIV – cell-based culture quadrivalent influenza vaccine; HD-QIV – high dose-quadrivalent influenza vaccine; IIV – inactivated influenza vaccine; QIV – quadrivalent influenza vaccine; RIV4 – recombinant HA quadrivalent influenza vaccine; TIV – trivalent influenza vaccine
*As indicated by the ECDC Vaccine Scheduler.
Note: Vaccines listed under "Vaccine type offered" reflect the vaccines offered in national-level vaccination programmes.

2.6 Discussion

Annual vaccination is an important preventive measure to reduce the burden associated with seasonal influenza. While elimination of influenza A is not feasible, annual influenza vaccination programmes aim to reduce the burden on health systems typically by prioritising those most at risk of severe disease for vaccination and or those who live with them or who are involved in their care (for example, healthcare workers).[3]

There are a range of IIVs available including a number of enhanced IIVs that have been developed specifically to improve vaccine effectiveness in individuals who are at higher risk of a suboptimal immune response. As of April 2024, there are three enhanced QIVs[31-33] authorised centrally by the EMA and a fourth enhanced QIV (a HD-QIV) authorised nationally by the HPRA in Ireland.[34] Additionally, there are three standard QIVs authorised by the HPRA,[41-43] of which two[42, 43] were marketed in Ireland and funded as part of the 2023-2024 HSE Seasonal Influenza Vaccination Programme.[92] It is worth noting that mRNA-based influenza vaccines are also in development. However, at the time of this assessment, these are still being evaluated through clinical trials and none have received a marketing authorisation from the EMA.

All EU/EEA countries and the UK have influenza vaccination programmes which include those aged 65 years and older. There is substantial heterogeneity among countries in terms of the type of vaccine used and whether vaccinations are funded through national health systems. A review of data published by the ECDC and websites of public health agencies for the target population found that for the 2023-2024 influenza season 19 out of 31 countries offer standard IIVs, four countries offer enhanced IIVs and eight countries offer a combination of standard IIVs and enhanced IIVs. Overall, 24 out of 31 countries fully fund influenza vaccinations for the target population, three partly fund influenza vaccinations for the target population, three countries do not fund influenza vaccinations for the target population and funding in one country varies by region.[46] Of the 10 countries that fund (fully or in part) an enhanced IIV, six of these specifically fund a HD-QIV, one reimburses an aQIV, one reimburses an aQIV, HD-QIV or ccQIV, one reimburses an aQIV, RIV4 or ccQIV, and one reimburses all four enhanced IIVs (aQIV, HD-QIV, RIV4 and ccQIV). Given the additional cost of the enhanced IIVs (see Chapter 6), a number of these countries restrict the availability of the enhanced IIV to those at highest risk within the target population, that is, by age (for example, those aged 75 years and older) or by setting (for example, those residing in long-term care facilities).

Differences in funding policy may reflect differences in the demographics and disease burden of influenza in the different countries. Additionally, since vaccination policy and funding in many countries are also influenced by the cost effectiveness and or budget impact of the decisions, it may also reflect differences in either vaccine or healthcare acquisition costs or differences in competing demands for healthcare resources. The burden of influenza in Ireland is explored in detail in Chapter 3 and the cost effectiveness and budget impact of switching from a standard IIV to an enhanced IIV is explored in detail in Chapter 6.

3 Epidemiology and Burden of Disease

Key points

- Influenza is a seasonal contagious respiratory illness. Although in many cases the symptoms are mild, complications can occur. All population groups are impacted during influenza seasons, although proportions vary from one year to another, depending on the circulating viruses and population immunity.
- Influenza incidence data were sourced from the Health Protection Surveillance Centre (HPSC) in Ireland by influenza season for the period 2010-2011 to 2022-2023. Hospital utilisation data were sourced from the Hospital In-Patient Enquiry (HIPE) system per calendar year for the period 2010 to 2022. Estimated averages exclude the seasons influenced by COVID-19 (2020-2021 and 2021-2022) as these data were not considered to be representative.
- HPSC data indicate that for the period 2010-2011 to 2022-2023, for those aged 65 years and older there has been year-on-year variability in terms of the rates of:
    - notified influenza cases (range: 25.0 to 718.5 per 100,000)
    - laboratory-confirmed influenza-related hospital admissions (range: 6.7 to 352.1 per 100,000)
    - hospital admissions with an intensive care unit (ICU) stay (range: 0.9 to 16.9 per 100,000)
    - influenza-related mortality (range: 1.7 to 24.9 per 100,000).
- When disaggregated by five-year age band, HPSC data for a number of indicators indicate that burden generally increases with age, with evidence of substantial year-on-year variability within each age band. For the 2022-2023 season, data for which are provisional, the rate of:
    - notified influenza cases ranged from 381.6 per 100,000 (65 to 69 years) to 1,495.1 per 100,000 (≥85 years)
    - laboratory-confirmed influenza-related hospital admissions ranged from 137.8 per 100,000 (65 to 69 years) to 580.3 per 100,000 (≥85 years)
    - laboratory-confirmed influenza-related hospital admissions with an ICU stay ranged from 3.7 per 100,000 (80 to 84 years) to 19.1 per 100,000 (75 to 79 years)
    - influenza-related deaths ranged from 7.1 per 100,000 (65 to 69 years) to 102.1 per 100,000 (≥85 years).

- As not all influenza cases are laboratory-confirmed, data relating to influenza-like illness (ILI) consultations in those aged 65 years and older were obtained from the HPSC in Ireland and used as an indication of the total burden on primary care. For the period 2010-2011 to 2022-2023 (excluding the seasons influenced by COVID-19), the ILI consultation rate ranged from 263.4 to 1,062.6 per 100,000 for the winter period. For the 2022-2023 season alone, the ILI consultation rate was 899.6 per 100,000 (n=331) in the winter period.
- HIPE data showed substantial variability over time in relation to the number of discharges, hospital length of stay (LOS) and total bed days. For those aged 65 years and older, data showed that between 2010 and 2022 there were, on average:
    - 441 (range: 14 to 1,407) discharges per annum with a primary diagnosis of influenza. The mean hospital LOS was nine days and the mean total bed days was 3,853 days per annum.
    - 38 (range: 10 to 84) discharges per annum with a primary diagnosis of influenza that included an ICU stay. The mean hospital LOS was eight days and the mean total bed days associated with these discharges was 290 days per annum.
    - 351 (range: 16 to 1,282) discharges per annum with a secondary diagnosis of influenza.
- The cost of acute hospital care was estimated using Diagnosis Related Groups (DRGs). The average cost of the DRGs related to influenza was approximately €6.03 million per annum in those aged 65 years and older.
- It is acknowledged that these data are likely an underestimate as not all influenza cases are tested and some discharges may not be coded. While there is an apparent trend of increasing incidence over time, this may reflect changing practices regarding testing.
- The influenza-related morbidity and mortality observed are in the context of an existing seasonal influenza immunisation programme which offers a standard quadrivalent influenza vaccine to those aged 65 years and older.
    - For the 2022-2023 season, the overall seasonal influenza vaccination uptake in those aged 65 years and older was 76.5%, with evidence that uptake increases with age.
    - However, it is not known what proportion of the observed morbidity and mortality occurred in those who were not vaccinated.

3.1 Introduction

This chapter describes the epidemiology of seasonal influenza and the burden of disease in Ireland, EU/EEA countries and the UK among adults aged 65 years and older.

Influenza is a contagious respiratory illness. In many cases the disease is mild, with symptoms such as chills, fever and fatigue. However, influenza can also result in serious complications, particularly in vulnerable individuals like young children, older adults (that is, those aged 65 years and older), pregnant women and individuals with medical conditions such as asthma, diabetes or heart disease.[13] Influenza viruses can be detected in most infected persons beginning one day before symptoms develop and up to five to seven days after symptom onset. People with influenza are most contagious in the first three to four days after their illness begins; however, infants and people with weakened immune systems may be contagious for longer than seven days.[93]

Influenza is largely contracted via droplets and contact as people sneeze or cough. It can also spread indirectly through respiratory emissions such as on tissues and hands; on average, two non-immune individuals will become infected from an infectious person. Given that the influenza viruses constantly evolve, protective immunity arising from either prior exposure or through vaccination is not life-long. This means that a large proportion of the population is susceptible to infection each season.[15]

In the Northern Hemisphere, the influenza season commences in October and can continue through to May the following year. In temperate regions, influenza activity generally peaks during the winter months (mostly between January and February); however, peaks can occur earlier. Influenza severity each season varies and depends on the circulating influenza virus type and subtype and influenza vaccine match and mismatch.[94]

Research has shown cold temperatures are a major determinant favouring both influenza A and influenza B. This could be due to a variety of reasons, such as a host's increased susceptibility to infection, viral shedding and longer periods of time spent indoors.[95] The highest burden of disease during seasonal epidemics is attributable to type A viruses, but both types A and B can cause epidemics and lead to significant disease and deaths. During influenza seasons all age groups are affected although proportions vary from one year to another, depending on population immunity and dominating viruses.

3.2 Data sources

The focus of this HTA is on seasonal influenza, which can be acquired at any time of year, but is most common in winter months. As noted, in the Northern Hemisphere, the influenza season commences in October and continues through to May. Surveillance of influenza refers to the collection, aggregation and analysis of influenza activity information for a defined population for a specified period of time. In Ireland, influenza surveillance occurs year-round and involves collection of both clinical and virological data. Clinical surveillance monitors the impact of the illness on the health service and the community, while virological surveillance confirms that influenza is circulating and also identifies the current strain.[96]

Incidence of influenza in the community in Ireland is estimated from data obtained from the Health Service Executive's (HSE's) sentinel surveillance programme for influenza, one of several sentinel general practice surveillance programmes for infectious diseases in Ireland.[97] Influenza activity is monitored by season. Each year, the international surveillance period runs from October (week 40) of one year to May (week 20) the following year, although most countries including Ireland monitor influenza all year round.[98] The Health Protection Surveillance Centre (HPSC), in partnership with the Irish College of General Practitioners (ICGP) and the National Virus Reference Laboratory (NVRL), have established a network of computerised sentinel general practices (across all HSE Areas) that report on a weekly basis the number of patients who consulted with influenza-like illness (ILI). In October 2023, this network was extended to also include those consulting with acute respiratory infection (ARI). At the time when data for this assessment were extracted, this network comprised 90 computerised sentinel general practices; as of May 2024, this has increased to 100 general practices. In this context, ILI is characterised by the sudden onset of symptoms consistent with influenza with a temperature of 38°C or more, in the absence of any other disease, with at least two of the following: dry cough, headache, sore muscles and a sore throat. Acute respiratory infection (ARI) is characterised as sudden onset of symptoms and at least one of the following four respiratory symptoms: cough, sore throat, shortness of breath, coryza and a clinician's judgement that the illness is due to an infection.

At the time when data were extracted for this assessment, the combined patient population in these sentinel general practices was approximately 10% of the national population (it is now approximately 18% of the national population) and it is considered to be nationally representative in terms of demographics and geographic distribution. GPs in sentinel practices send combined nose and throat swabs to the NVRL each week. The NVRL routinely tests respiratory specimens, including those from sentinel practices, for influenza and a panel of other respiratory viruses. It should be noted that, for the sentinel programme, primary care practices are advised

to sample the first five cases presenting each week. As such, the sentinel data may underestimate the total incidence.

Other surveillance systems set up to monitor influenza activity in Ireland include:

- surveillance of all confirmed influenza notifications, including hospitalisation status reported to the Computerised Infectious Disease Reporting (CIDR) system in Ireland
- enhanced surveillance of all critical care patients with confirmed influenza
- surveillance of all reported influenza deaths
- surveillance of all calls to GP out-of-hours (OOHs) centres, monitored for self-reported influenza and cough
- all-cause excess mortality monitoring associated with the European mortality monitoring group (EuroMOMO)
- acute respiratory infections and influenza outbreak surveillance.[96]

While not specific to influenza, it is noted that there is also sentinel surveillance of severe acute respiratory infections (SARI) in hospital inpatients. This was implemented in one tertiary care adult hospital in July 2021. The hospital local catchment area is in the Dublin and greater Dublin area, accounting for approximately 7% of the national population. SARI cases are identified from Emergency Department admissions which meet the SARI case definition, based on presenting symptoms. The European Centre for Disease Prevention and Control (ECDC) clinical SARI case definition is currently used for the SARI surveillance project in Ireland. A clinical SARI case is defined as a hospitalised (that is, hospitalised for at least 24 hours) person with acute respiratory infection, with at least one of the following symptoms (onset within 14 days prior to hospital admission): cough, fever, shortness of breath, sudden onset of anosmia, ageusia or dysgeusia.

As there is little difference in the presenting symptoms of a number of respiratory pathogens, virological confirmation is required to identify that influenza is the causative agent. The NVRL can detect and identify if influenza A and or B viruses are circulating. Further identification of subtypes of influenza A isolates is also carried out. Samples received at the NVRL undergo polymerase chain reaction testing, cell culture and virus isolation.[96]

For this HTA, data were gathered from the Sentinel GP network, CIDR and the NVRL for 13 influenza seasons (2010-2011 to 2022-2023); these data were provided to HIQA by the HPSC. For the influenza surveillance data, the term winter period is used to refer to data reported for week 40 of one calendar year to week 20 of the next, and the term summer period is used to refer to weeks 21 to 39 of the same year. It should be noted that the winter period precedes the summer period.

Data were obtained in August 2023. Data for seasons 2021-2022 and 2022-2023 are provisional (that is, these data are being updated retrospectively to account for data cleaning at the local level or deaths that have been reported in the interim). For the 2022-2023 season, where data are presented for those aged 65 years and older, these data represent week 40 to week 20, but as noted above, these data are provisional. Where data are presented for those aged 0 to 64 years, these were limited to week 40 to week 13 and are therefore incomplete. Data for summer 2023 include data from week 21 to week 30 (except for sentinel GP ILI consultation data which includes data up to and including week 32); as such, these data are also incomplete (that is, these data were still being collected at the time data were requested).

Data from the Hospital In-Patient Enquiry (HIPE) system were also gathered to understand the nature of influenza hospitalisations (for example, complications of the disease and hospital length of stay (LOS)). These data were provided by calendar year, not influenza season. Data from the HIPE system in Ireland were used to examine hospital discharges with and without an intensive care unit (ICU) stay for patients aged 65 years and older with a primary or secondary diagnosis of influenza and or upper respiratory infections with ICD-10 codes J09, J10 and J11. 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.[99] Since data were provided by calendar year rather than by influenza season, they may not fully capture changes in disease severity across seasons. Hospital admissions with an ICU stay are a subset of all hospital admission data.

It is also important to note that while influenza is a notifiable disease, in reality many cases may not be identified or subsequently notified. In this analysis, notified cases are used as a measure of impact on the healthcare system, reflecting interactions with a GP and or hospital. However, it is acknowledged that this is an underestimation of the total burden of influenza as these cases represent a subset of those who sought medical care for influenza or ILI. ILI consultation rates were also reported to provide context on the number of ILI-related GP consultations that occur per season. While primary care practices are advised to sample the first five ILI cases presenting each week, all ILI consultations are recorded. As noted above, as of October 2023, ARI cases are also now sampled. Finally, where data are reported per 100,000 population, this is based on a population of 535,393 people aged 65 years and older for seasons 2010-2011 to 2014-2015 (based on Census 2011 data)[100] and a population of 637,567 people aged 65 years and older for seasons 2015-2016 to 2022-2023 (based on Census 2016 data).[101]

3.3 Incidence of influenza

Data related to the incidence of influenza in Ireland and in the EU/EEA are presented in Sections 3.3.1 and 3.3.2, respectively.

3.3.1 Incidence of influenza in Ireland

Table 3.1 reports the types and subtypes of a subset of all notified influenza cases from the 2010-2011 season to the 2022-2023 season in those aged 65 years and older; these data were only available for the winter period. Not all influenza cases are typed or subtyped by the NVRL. As such, type and subtype data are reported as absolute numbers, not rates per 100,000, and represent a subset of all notified cases. Type and subtype data were only reported for notified influenza cases, not influenza-related hospital admissions, ICU admissions or deaths. Due to the small sample sizes for seasons 2010-2011 to 2012-2013, the estimated relative proportions are imprecise. Considering the relative frequencies by influenza type, the data suggest a predominance of influenza A, with the exception of 2017-2018 when 57% of the notified cases typed by the NVRL were influenza B. Excluding the 2020-2021 and 2021-2022 seasons, which were clearly influenced by the COVID-19 pandemic, there appears to have been an increase in the number of notified cases that are typed by the NVRL.

Table 3.1 Reported type and or subtypes of notified influenza cases from 2010-2011 to 2022-2023 in those aged 65 years and older (winter period)

Influenza season	Influenza A (not subtyped) %	Influenza A(H3) %	Influenza A(H1)pdm09 %	Influenza B %	Total number of influenza cases typed and or subtyped (n)
2010-2011	14	4	55	26	**134**
2011-2012	42	49	0	9	**183**
2012-2013	11	61	6	23	**426**
2013-2014	23	65	11	1	**598**
2014-2015	20	57	3	20	**958**
2015-2016	16	1	51	32	**675**
2016-2017	49	48	0	2	**1,385**
2017-2018	25	15	2	57	**4,495**
2018-2019	69	11	19	1	**1,594**
2019-2020	79	15	2	4	**3,191**
2020-2021	-	-	-	-	**-**
2021-2022	80	20	0	0	**546**
2022-2023	83	7	8	2	**4,583**

Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional. There were no notified influenza cases for the following categories: 'Influenza A(H1)pdm09 and A(H3)', 'Influenza A and B', 'Influenza type and or subtype not reported'.
Source: Health Protection Surveillance Centre.

Notified influenza incidence rates for those aged 65 years and older are reported in Table 3.2. Considering influenza seasons since 2010-2011, and excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), notifications for the winter period have varied substantially from year to year (mean: 1,656; range: 134 to 4,581) corresponding to a notification rate ranging from 25.0 to 718.5 per 100,000 in those aged 65 years and older. Winter notification rates were consistently and substantially higher than those reported for the summer period (range: 0.0 to 16.0 per 100,000).

Provisional data for the most recent season (2022-2023) indicate notified case rates of 718.5 per 100,000 (n=4,581) for the winter period versus 1.1 per 100,000 (n=7) for the summer period. The notified case rate reported for 2022-2023 was the highest observed across all 13 seasons; this figure may increase further when these data are finalised.

Table 3.2 Laboratory-confirmed influenza case rates per 100,000 from 2010-2011 to 2022-2023 in those aged 65 years and older in Ireland (winter period and summer period)

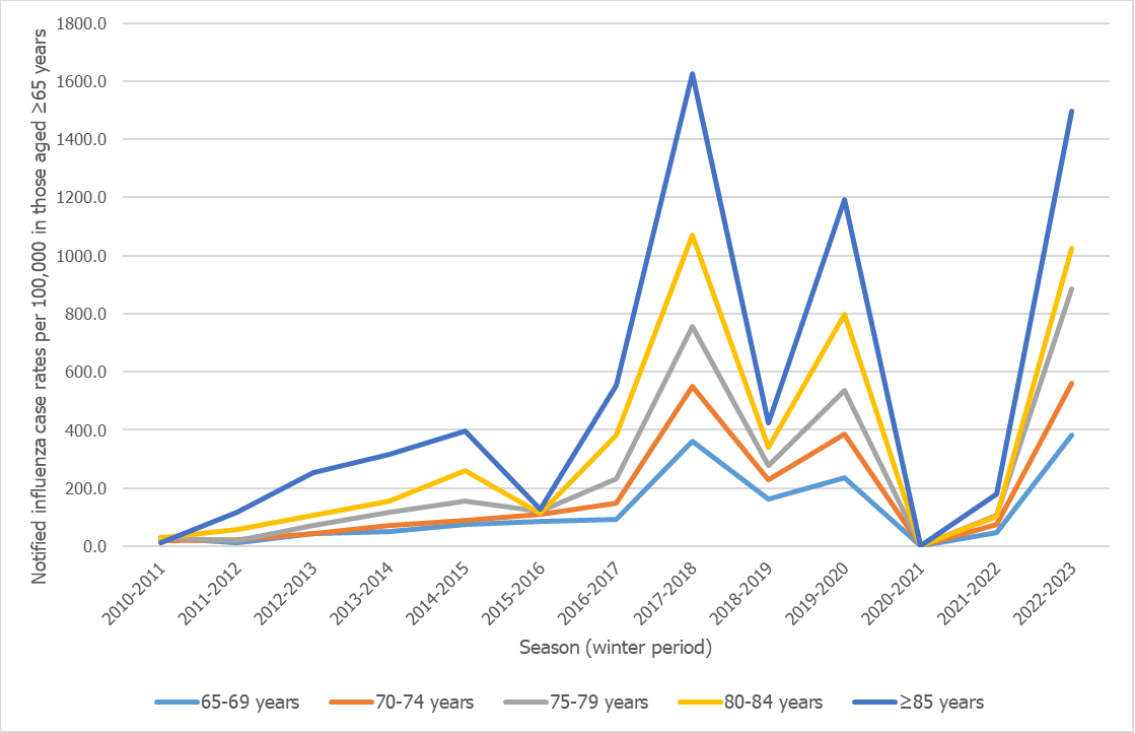
Season (winter period)	Notified cases		Season (summer period)	Notified cases	
	n	Rate per 100,000		n	Rate per 100,000
2010-2011	134	25.0	2011	0	0.0
2011-2012	183	34.2	2012	6	1.1
2012-2013	426	79.6	2013	7	1.3
2013-2014	598	111.7	2014	2	0.4
2014-2015	958	150.3	2015	9	1.4
2015-2016	675	105.9	2016	10	1.6
2016-2017	1,385	217.2	2017	32	5.0
2017-2018	4,495	705.0	2018	15	2.4
2018-2019	1,594	250.0	2019	66	10.4
2019-2020	3,191	500.5	2020	0	0.0
2020-2021	0	0.0	2021	0	0.0
2021-2022	546	85.6	2022	102	16.0
2022-2023	4,581	718.5	2023	7	1.1
Mean per annum*	**n=1,656**		**Mean per annum***	**n=23**	

*Mean per annum excludes the seasons influenced by COVID-19 (2020-2021 and 2021-2022).
Note: Data for the 2021-2022 and 2022-2023 (winter period) influenza seasons and the 2022 (summer period) influenza season are provisional. Data for the 2023 (summer period) influenza season are incomplete.
Source: Health Protection Surveillance Centre.

In general, the incidence of notified influenza cases has increased over time in those aged 65 years and older. However, it is unclear whether this is solely due to an increase in the number of cases or if it is also influenced by an increasing proportion of cases being tested. Caution is therefore required in inferring temporal trends based on the data presented.

Data relating to notified influenza cases were also considered by five-year age band and season (winter period only) for those aged 65 years and older (Figure 3.1). While there is evidence of year-on-year variability in notified influenza case rates for all age bands, rates typically increased with age, with the highest rates observed in those aged 85 years and older. Based on provisional data for the 2022-2023 season, the notified influenza case rate was 381.6 per 100,000 (n=806) in those aged 65 to 69 years, 562.0 per 100,000 (n=912) in those aged 70 to 74 years, 884.2 per 100,000 (n=1,021) in those aged 75 to 79 years, 1,026.7 per 100,000 (n=832) in those aged 80 to 84 years and 1,495.1 per 100,000 (n=1,010) in those aged 85 years and older.

Figure 3.1 Notified influenza case rates per 100,000 from 2010-2011 to 2022-2023 in those aged 65 years and older, reported by five-year age band and season (winter period)



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

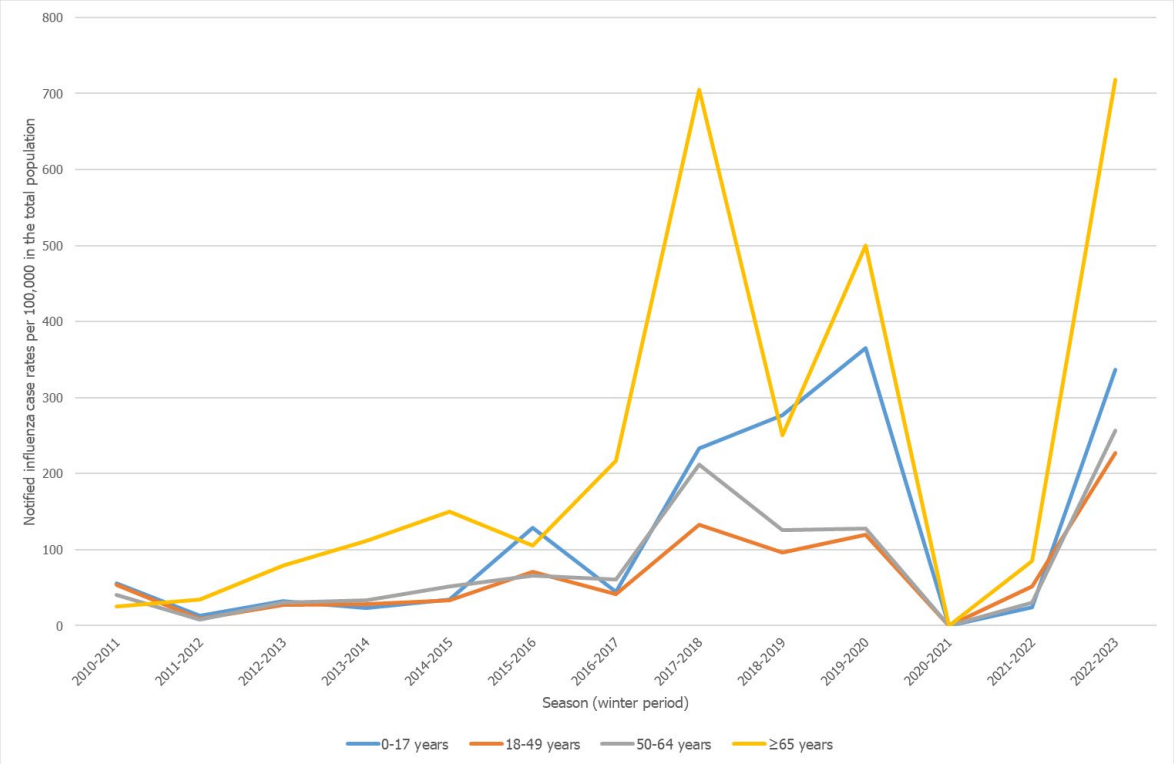
For context, Figure 3.2 provides a summary of the notified influenza case rate during the winter period for the total population in Ireland, reported by the following age bands: 0 to 17 years, 18 to 49 years, 50 to 64 years and 65 years and older. In ten of the 13 seasons, the highest rates were observed in those aged 65 years and older.

Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), the average number of notified cases per annum occurring in those aged 0 to 17 years was 1,665 (range: 154 to 4,348); it was 1,628 (range: 202 to 4,831) in those aged

18 to 49 years; 738 (range: 61 to 2,078) in those aged 50 to 64 years; and for those aged 65 years and older it was 1,656 (range: 134 to 4,581). On average, 29% (range: 6% to 42%) of all notified influenza cases occurred in those aged 65 years and older per annum. While the proportion of those aged 65 years and older in the total population in Ireland has increased over time, from 11.7% in 2011[100] to 15.1% in 2022,[102] these data highlight the disproportionate burden in older people relative to their proportion of the total population.

Based on provisional data for the 2022-2023 season, the notified influenza case rate was 336.4 per 100,000 (n=4,005) in those aged 0 to 17 years, 227.4 per 100,000 (n=4,831) in those aged 18 to 49 years, 256.9 per 100,000 (n=2,078) in those aged 50 to 64 years, and 718.5 per 100,000 (n=4,581) in those aged 65 years and older; meaning, those aged 65 years and older accounted for 30% of all notified influenza cases in the 2022-2023 season.

Figure 3.2 Notified influenza case rates per 100,000 from 2010-2011 to 2022-2023 for the total population reported by age group and influenza season (winter period)



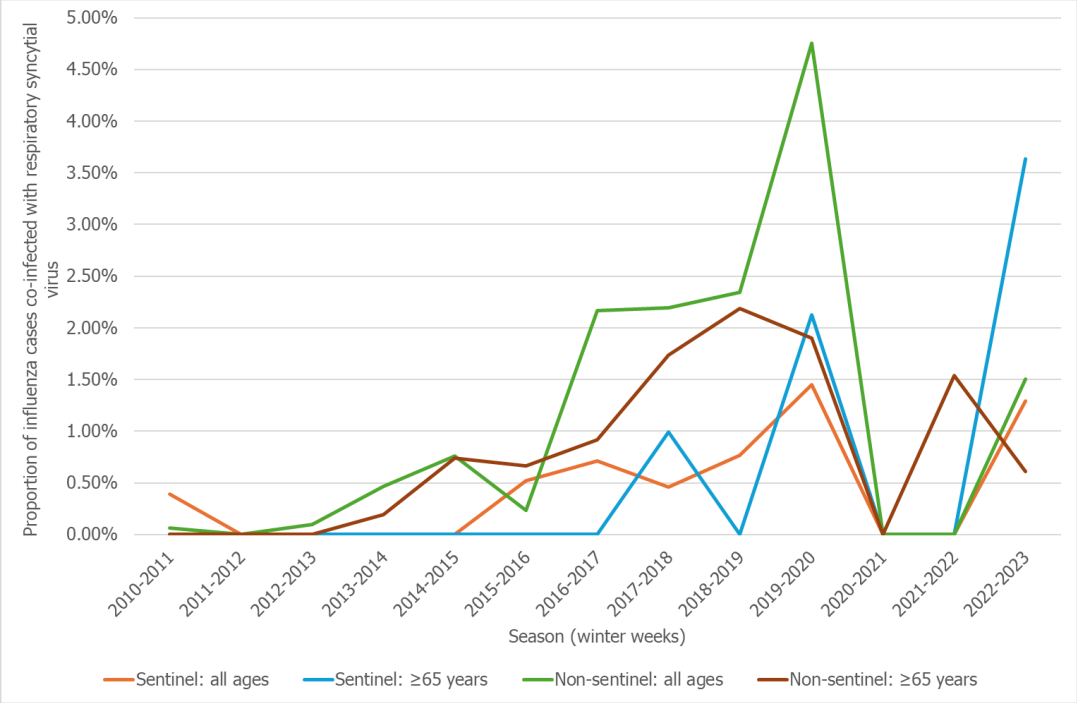
Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional; data for those aged 0 to 64 years represent week 40 to week 13 of the 2022-2023 season; data for those aged 65 years and older represent week 40 to week 20 of the 2022-2023 season.
Source: Health Protection Surveillance Centre.

Co-infection with respiratory syncytial virus or SARS-CoV-2

Data on the number of notified influenza cases co-infected with either respiratory syncytial virus (RSV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were provided by the HPSC. These data were extracted from sentinel and non-sentinel surveillance systems and reported separately for all ages and those aged 65 years and older. Rates of co-infection were low.

Of all the influenza cases reported through the sentinel surveillance system from seasons 2010-2011 to 2022-2023, 0.57% (n=30) and 0.94% (n=4) were co-infected with RSV in all ages and in those aged 65 years and older, respectively. For the same time period, of all the influenza cases reported through the non-sentinel surveillance system, 1.76% (n=345) and 1.16% (n=68) were co-infected with RSV in all ages and those aged 65 years and older, respectively. Figure 3.3 provides a summary of the proportion of influenza cases co-infected with RSV, reported through the sentinel and non-sentinel surveillance systems for seasons 2010-2011 to 2022-2023. It should be noted that sentinel data include up to five swabs per GP practice per week and non-sentinel data are a subset of samples sent to the NVRL for testing. As such, these do not represent the total burden of influenza (and co-infections) per season.

Figure 3.3 Proportion of influenza cases co-infected with respiratory syncytial virus, reported through the sentinel and non-sentinel surveillance systems for seasons 2010-2011 to 2022-2023



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

Data for influenza cases co-infected with SARS-CoV-2 were only available for seasons 2021-2022 and 2022-2023. Rates of co-infection were 2.31% (n=16) in all ages and 1.67% (n=1) in those aged 65 years and older.

3.3.2 Incidence of influenza in EU/EEA countries

Since 2014, influenza surveillance in Europe has been jointly coordinated by the World Health Organization (WHO) Regional Office for Europe and the ECDC. Surveillance data from the 53 countries of the WHO European Region (which includes the 30 EU/EEA countries) are submitted to a joint ECDC/WHO database hosted in the European Surveillance System. Influenza surveillance data are reported weekly during the influenza season (that is, week 40 to week 20 of the following year).[98]

In the 2020-2021 influenza season, global influenza activity levels were extremely low. This was considered potentially attributable to the effectiveness of non-pharmaceutical interventions recommended during the COVID-19 pandemic (that is, social distancing, restricted travel, hand hygiene and mask-wearing) in limiting transmission. As a result, population immunity against influenza was expected to be lower during the subsequent 2021-2022 influenza season.[103] However, the ECDC seasonal influenza annual epidemiological report for 2021-2022 reported that, while this season marked the return of influenza virus activity, the circulation and timing differed, with the seasonal pattern showing an unprecedented later onset and overall shorter duration compared with all seasons since 2009. This might have been influenced by the COVID-19 pandemic and measures implemented in the countries during the winter period, leading to late activity when measures were lifted.[104]

In the subsequent 2022-2023 season, influenza virus activity returned to almost pre-pandemic levels. This season was characterised by an earlier start and earlier peak in positivity compared with the four previous seasons. The percentage of positive specimens peaked at 42% in week 51/2022. This was followed by a decrease until week 4/2023 when it reached 22% positivity before rising again to fluctuate around 28% positivity between week 5/2023 to week 12/2023. The threshold of less than 10% positivity was passed in week 17, which indicated the end of the seasonal influenza epidemic.[105]

3.4 Burden of disease

3.4.1 General practitioner attendance in Ireland

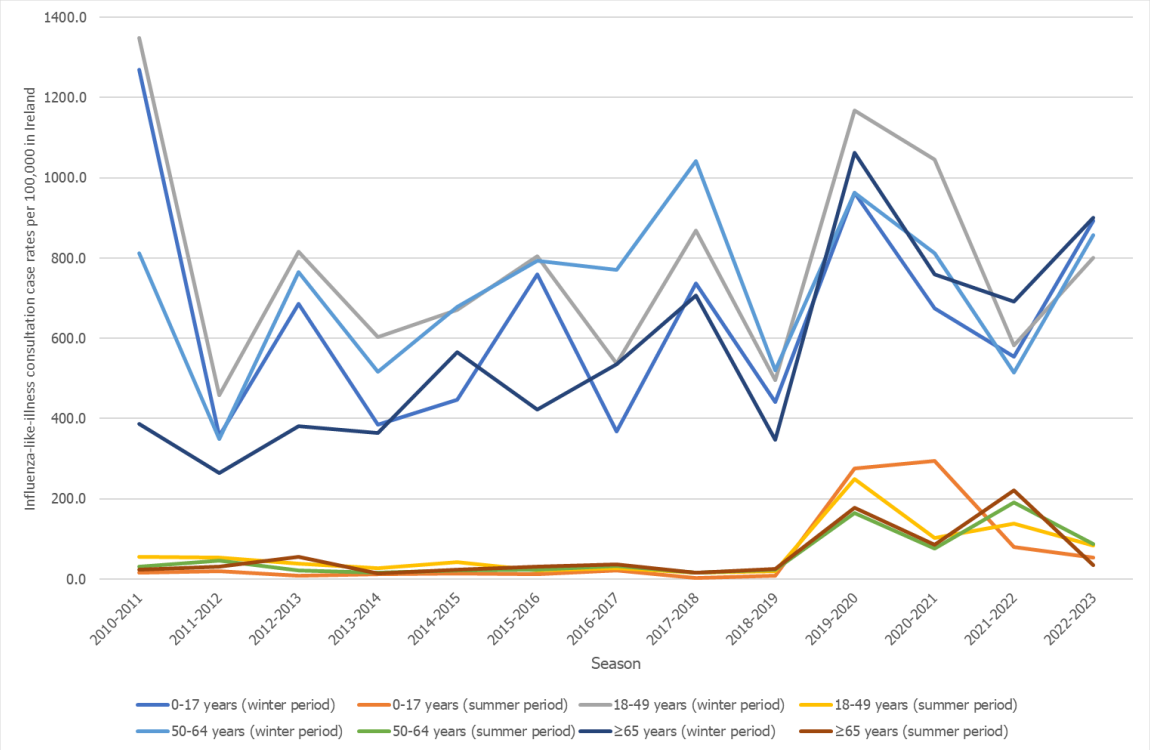
As described in Section 3.2.1, ILI consultation data from sentinel general practices in primary care were obtained to provide an indication of the burden of medically-attended influenza and ILI in primary care. It is noted that, for the sentinel

database, while primary care practices only sample the first five ILI consultations each week, all ILI consultations undertaken in primary care are counted.

ILI consultation rates per 100,000 for 13 seasons commencing in 2010-2011 are reported in Figure 3.4 for both the winter and summer periods for the total population. Excluding the seasons influenced by COVID-19, there has been substantial variability in terms of the rates of ILI consultations reported in all age groups during the winter and summer periods over the 13 seasons. Consultation rates were consistently higher in the winter period across all seasons and age groups. During the winter period, ILI consultation rates have ranged from 357.1 to 1,268.8 per 100,000 in those aged 0 to 17 years, 458.4 to 1,347.3 per 100,000 in those aged 18 to 49 years, 348.6 to 1,041.2 per 100,000 in those aged 50 to 64 years, and 263.4 to 1,062.6 per 100,000 in those aged 65 years and older. During the summer period, ILI consultation rates have ranged from 2.6 to 79.2 per 100,000 in those aged 0 to 17 years, 16.8 to 139.0 per 100,000 in those aged 18 to 49 years, 16.4 to 190.7 per 100,000 in those aged 50 to 64 years, and 13.4 to 220.8 per 100,000 in those aged 65 years and older.

Considering specifically those aged 65 years and older, there appears to be a trend for increasing incidence of ILI consultations over time (although this is not statistically significant). For the 2022-2023 season alone, the ILI consultation rate was 899.6 per 100,000 (n=331) in those aged 65 years and older for the winter period.

Figure 3.4 Influenza-like-illness consultation rates per 100,000 from 2010-2011 to 2022-2023 for the total population, reported by season and age group (winter and summer period)



Note: Data for the 2021-2022 and 2022-2023 (winter period) influenza seasons and 2022 (summer period) influenza season are provisional. Data for the 2023 (summer period) influenza season are incomplete.
Source: Health Protection Surveillance Centre.

3.4.2 Complications and hospitalisations in Ireland

Surveillance data relating to SARI for those aged 65 years and older were gathered for the seasons 2021-2022 and 2022-2023. Rates of SARI per 100,000 in Ireland for each five-year age band are presented in Table 3.3 for the winter and summer periods. Considering data for the winter periods, the reported SARI case rate consistently increased with increasing age. Lower case rates were observed in all age bands during the summer periods.

Table 3.3 Severe acute respiratory infection case rates per 100,000 for 2021-2022 and 2022-2023 in those aged 65 years and older, reported by five-year age band and season (winter and summer period)

Season	Severe acute respiratory infection case rates per 100,000 (absolute number)				
	65-69 years	70-74 years	75-79 years	80-84 years	≥85 years
2021-2022 (winter period)	163.4 (28)	343.5 (51)	499.1 (59)	890.8 (73)	807.4 (64)
2022 (summer period)	163.4 (28)	148.2 (22)	270.7 (32)	329.5 (27)	567.7 (45)
2022-2023 (winter period)	320.9 (55)	431.0 (64)	693.6 (82)	1220.3 (100)	1299.4 (103)
2023 (summer period)	116.7 (20)	101.0 (15)	169.2 (20)	219.6 (18)	126.2 (10)

Note: Data for the 2021-2022 and 2022-2023 (winter period) influenza seasons and 2022 (summer period) influenza season are provisional. Data for the 2023 influenza season are incomplete.
Source: Health Protection Surveillance Centre.

Influenza-related hospital admissions

Data sourced from the HPSC for the period 2010-2011 to 2022-2023 provided information relating to laboratory-confirmed influenza-related hospital admissions and laboratory-confirmed influenza-related hospital admissions that included an ICU stay; it should be noted that the latter are a subset of all laboratory-confirmed influenza-related hospital admissions. These data were provided per influenza season.

Considering influenza seasons since 2010-2011, and excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), influenza-related hospital admissions for the winter period have varied substantially from year to year (mean: 797; range: 36 to 2,245) corresponding to a rate ranging from 6.7 to 352.1 per 100,000 in those aged 65 years and older.

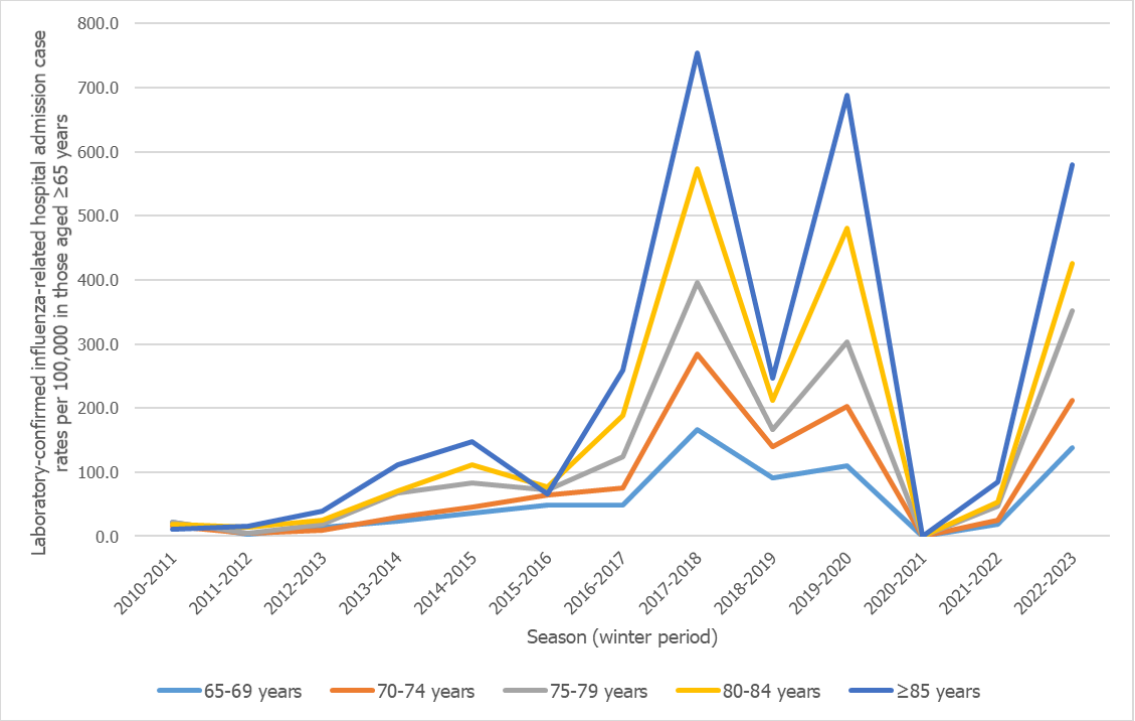
The average number of laboratory-confirmed influenza-related hospital admissions per annum (excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022)) and considering the winter period only, for those aged 65 years and older, were disaggregated by five-year age band. The estimated average per annum was 132 (range: 6 to 353) in those aged 65 to 69 years; 158 (range: 7 to 461) in those aged 70 to 74 years; 168 (range: 4 to 457) in those aged 75 to 79 years; 161 (range: 10 to 465) in those aged 80 to 84 years; and 178 (range: 6 to 509) in those aged 85 years and older.

Rates of laboratory-confirmed influenza-related hospital admissions during the winter period are reported for those aged 65 years and older disaggregated by five-year age band in Figure 3.5. From 2010-2011 to 2019-2020 there was a statistically significant increase in the rate of laboratory-confirmed influenza-related hospital

admissions in those aged 65 years and older ($p<0.05$). Additionally, the rate of laboratory-confirmed influenza-related hospitalisation increased with increasing age and was generally highest in the subgroup aged 85 years and older.

For the 2022-2023 season (data for which are provisional) the laboratory-confirmed influenza-related hospital admission rates reflect this trend. Specifically, rates were 137.8 per 100,000 (n=291) in those aged 65 to 69 years, 212.0 per 100,000 (n=344) in those aged 70 to 74 years, 352.5 per 100,000 (n=407) in those aged 75 to 79 years, 425.7 per 100,000 (n=345) in those aged 80 to 84 years, and 580.3 per 100,000 (n=392) in those aged 85 years and older.

Figure 3.5 Laboratory-confirmed influenza-related hospital admission rates per 100,000 from 2010-2011 to 2022-2023 in those aged 65 years and older, reported by five-year age band and season (winter period)



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

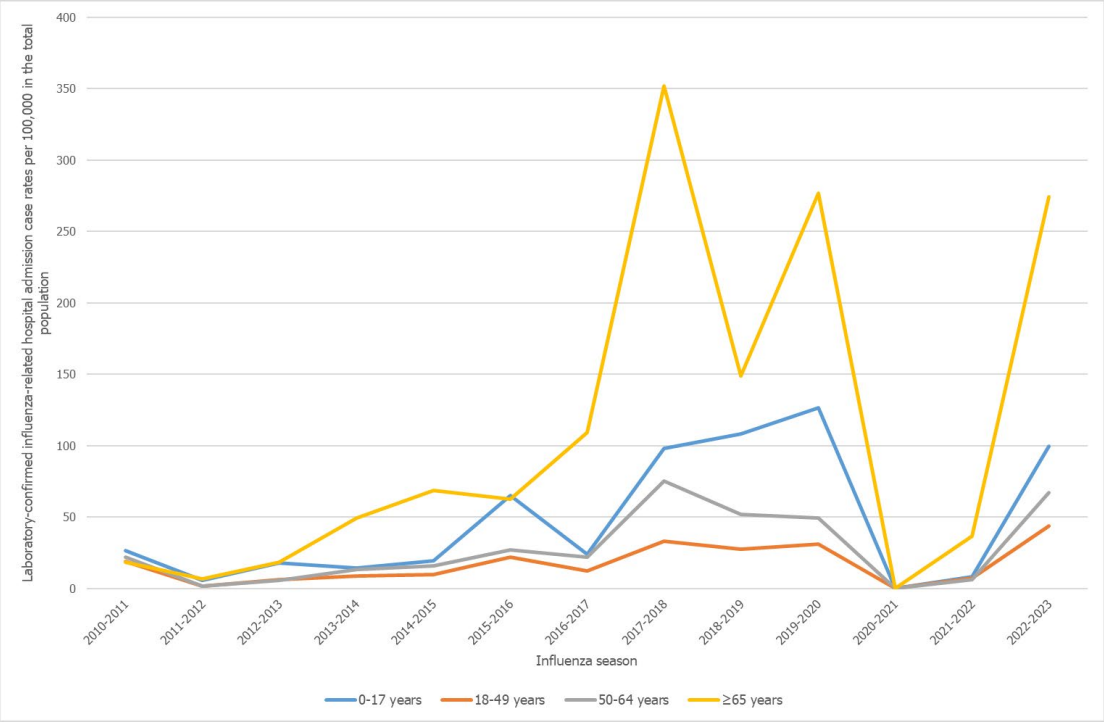
For context, information is provided relative to the total burden (all ages) of laboratory-confirmed influenza-related hospital admissions. In general, laboratory-confirmed influenza-related hospital admission rates were higher in those aged 65 years and older than in all other age groups (Figure 3.6).

Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), the average number of laboratory-confirmed influenza-related hospital admissions per annum was 652 (range: 67 to 1,508) in those aged 0 to 17 years, 416 (range: 31 to 929) in those aged 18 to 49 years, 255 (range: 13 to 608) in those aged 50 to 64

years and 797 (range: 36 to 2,245) in those aged 65 years and older. On average, 38% (range: 10% to 49%) of laboratory-confirmed influenza-related hospital admissions per annum occurred in those aged 65 years and older. Again, it is important to note that the proportion of the population aged 65 years and older has increased over time.

For the 2022-2023 season (data for which are provisional), the laboratory-confirmed influenza-related hospital admission rate was 99.4 per 100,000 (n=1,183) in those aged 0 to 17 years, 43.7 per 100,000 (n=929) in those aged 18 to 49 years, 67.3 per 100,000 (n=544) in those aged 50 to 64 years, and 279.0 per 100,000 (n=1,779) in those aged 65 years and older; meaning, those aged 65 years and older accounted for 40% of all influenza-related hospital admissions in the 2022-2023 season. As outlined in Section 3.2, however, it should be noted that data for those aged 0 to 64 years are incomplete (week 40 to week 13 only).

Figure 3.6 Laboratory-confirmed influenza-related hospital admission rates per 100,000 from 2010-2011 to 2022-2023 for the total population reported by age group and influenza season (winter period)



Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional; data for those aged 0 to 64 years represent week 40 to week 13 of the 2022-2023 season; data for those aged 65 years and older represent week 40 to week 20 of the 2022-2023 season.
Source: Health Protection Surveillance Centre.

Considering the population aged 65 years and older as a whole, there has been variability in the rates of laboratory-confirmed influenza-related hospital admissions

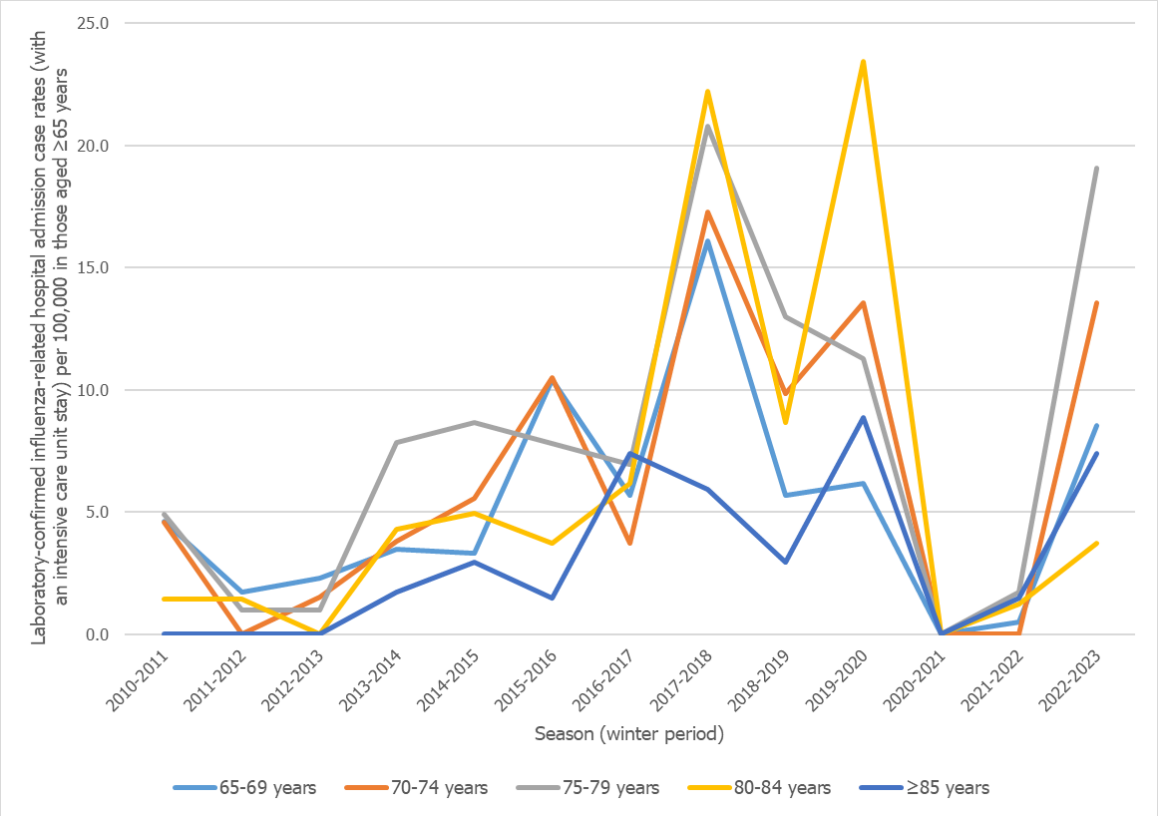
with an ICU stay (range: 0.9 to 16.9 per 100,000) across the seasons included in this HTA.

For the winter period alone, and excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), there was evidence of substantial variability in the number of laboratory-confirmed influenza-related hospital admissions with an ICU stay reported within each five-year age band. Across the period, the average number per annum was 13 (range: 3 to 34) in those aged 65 to 69 years, 12 (range: 0 to 28) in those aged 70 to 74 years, 11 (range: 1 to 24) in those aged 75 to 79 years, 6 (range: 0 to 19) in those aged 80 to 84 years and 2 (range: 0 to 6) in those aged 85 years and older.

Rates of laboratory-confirmed influenza-related hospital admissions with an ICU stay (winter period) for those aged 65 years and older are reported by five-year age band for the period from 2010-2011 to 2022-2023 in Figure 3.7. On average, approximately 5% of hospitalised cases aged 65 years and older had an ICU stay; however, within this cohort there was no apparent association between admission rates and age. From 2010-2011 to 2019-2020 there was a statistically significant ($p<0.05$) increase in the rate of laboratory-confirmed influenza-related hospital admissions which included an ICU stay in those aged 65 years and older. It is worth noting that the increase in hospital admissions involving an ICU stay may simply reflect the increase in all hospital admissions due to influenza.

For the 2022-2023 season (data for which are provisional), the rate of laboratory-confirmed influenza-related hospital admissions with an ICU stay was 8.5 per 100,000 (n=18) in those aged 65 to 69 years, 13.6 per 100,000 (n=22) in those aged 70 to 74 years, 19.1 per 100,000 (n=22) in those aged 75 to 79 years, 3.7 per 100,000 (n=3) in those aged 80 to 84 years and 7.4 per 100,000 (n=5) in those aged 85 years and older.

Figure 3.7 Laboratory-confirmed influenza-related hospital admission rates (which included an intensive care unit stay) per 100,000 from 2010-2011 to 2022-2023 in those aged 65 years and older, reported by five-year age band and season (winter period)



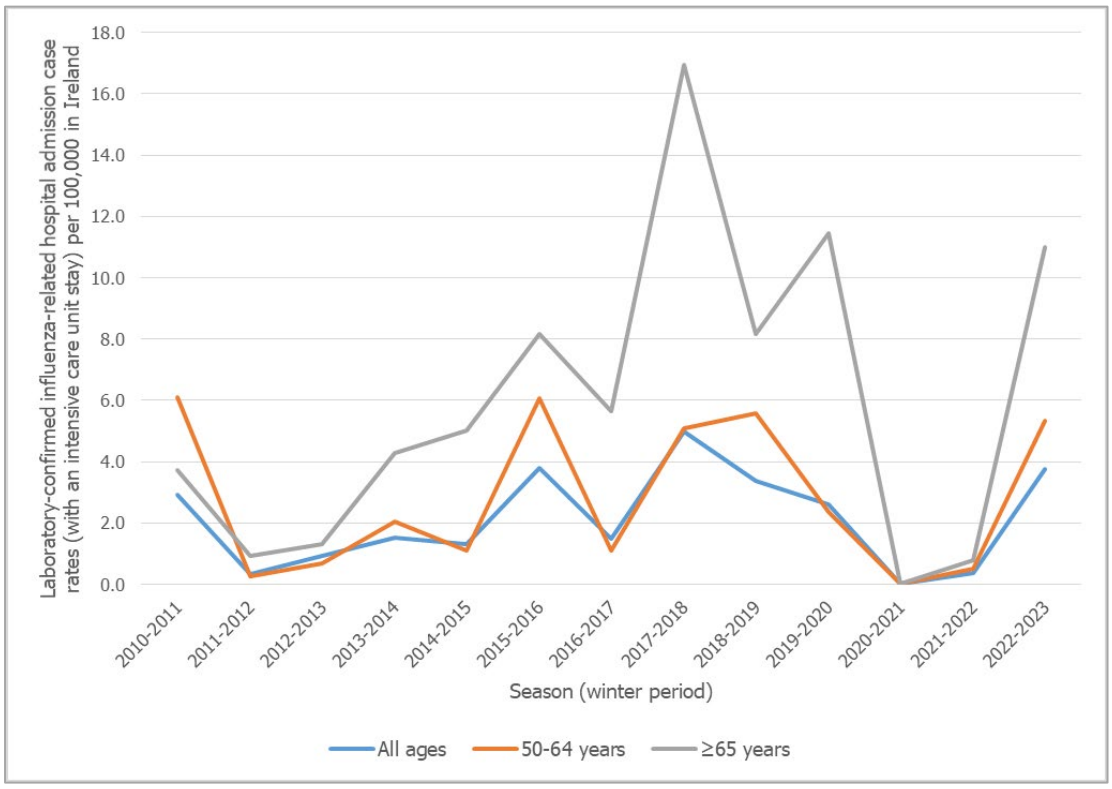
Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional.
Source: Health Protection Surveillance Centre.

For context, Figure 3.8 provides a summary of rates of laboratory-confirmed influenza-related hospital admissions with an ICU stay for the total population from 2010-2011 to 2022-2023. These data are reported for the winter period for the total population (that is, all ages), those aged 50 to 64 years and those aged 65 years and older. In general, rates of laboratory-confirmed influenza-related hospital admissions with an ICU stay were higher in those aged 65 years and older than in those aged 50 to 64 years.

Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), the average number of laboratory-confirmed influenza-related hospital admissions with an ICU stay per annum occurring in the total population was 116 (range: 15 to 237), 43 (range: 5 to 108) in those aged 65 years and older and 26 (range: 2 to 49) in those aged 50 to 64 years. On average, 37% (range: 15% to 59%) of laboratory-confirmed influenza-related hospital admissions with an ICU stay occurred in those aged 65 years and older per annum. Again, it is important to note that the proportion of the population aged 65 years and older has increased over time.

For the 2022-2023 season (data for which are provisional) the laboratory-confirmed influenza-related hospital admission with an ICU stay rate was 3.8 per 100,000 (n=185) in the total population, 5.3 per 100,000 (n=43) in those aged 50 to 64 years, and 11.0 per 100,000 (n=70) in those aged 65 years and older; meaning, those aged 65 years and older accounted for 38% of all influenza-related hospital admissions with an ICU stay in the 2022-2023 season.

Figure 3.8 Laboratory-confirmed influenza-related hospital admission rates (which included an intensive care unit stay) per 100,000 from 2010-2011 to 2022-2023, reported by age group and influenza season (winter period)



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

Hospital discharges and associated 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 influenza and or upper respiratory infections with ICD-10 codes J09, J10 and J11. As noted in Section 3.2, 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.[99] Data were provided by calendar year rather than by influenza season, so may not fully capture changes in disease severity across seasons.

Discharges with a primary diagnosis of influenza

Table 3.4 provides an overview of inpatient discharges with a primary diagnosis of influenza in the total population, from 2010 to 2022 presented by age band. Considering the total population, patients aged 65 years and older accounted for 34% of all discharges with a primary diagnosis of influenza. The highest mean annual number of discharges was observed in this age group (mean annual number of discharges: 441 (range: 14 to 1,407)). As noted, while the proportion of the population aged 65 years and older has increased over time, as of 2022, this population group represented only 15% of the total population in Ireland.[106]

Considering those aged 65 years and older only, 38% of the total number of discharges with a primary diagnosis of influenza were in those aged 80 years and older. The highest mean annual number of discharges was observed in those aged 70 to 74 years (mean annual number of discharges: 116 (range: 11 to 308)).

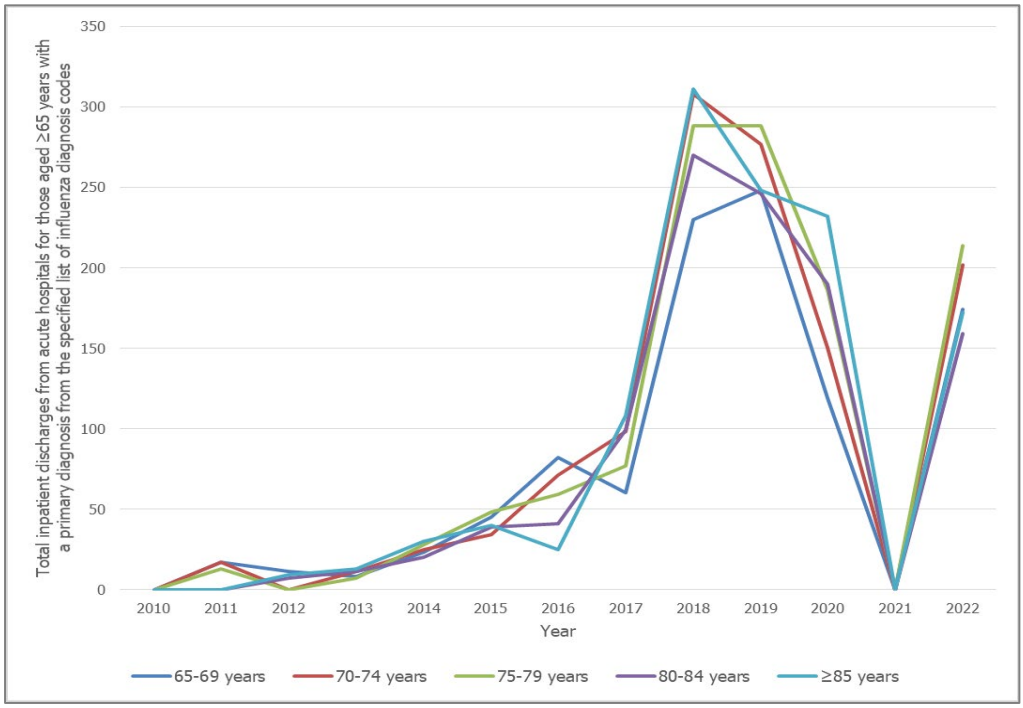
Table 3.4 Hospital discharges per calendar year for those with a primary diagnosis of influenza (2010 to 2022) by age band

Age band (years)	Total number of discharges*	Mean annual number of discharges (range)*
0-17	4,343	395 (27-1,500)
18-49	3,042	277 (42-717)
50-64	2,193	199 (17-571)
65+~	4,851	441 (14-1,407)
65-69	898	90 (8-248)
70-74	1,043	116 (11-308)
75-79	1,022	114 (7-288)
80-84	892	99 (7-270)
85+	956	106 (9-311)

Note: Hospital discharges associated with a primary diagnosis of influenza from the specified list of influenza diagnosis codes.
*Total and mean exclude the years 2020 and 2021 (which are not considered representative due to the influence of COVID-19).
~Reported values are higher than the sum of discharges broken down by age band due to suppression of cells for certain years.
Source: Hospital In-Patient Enquiry System.

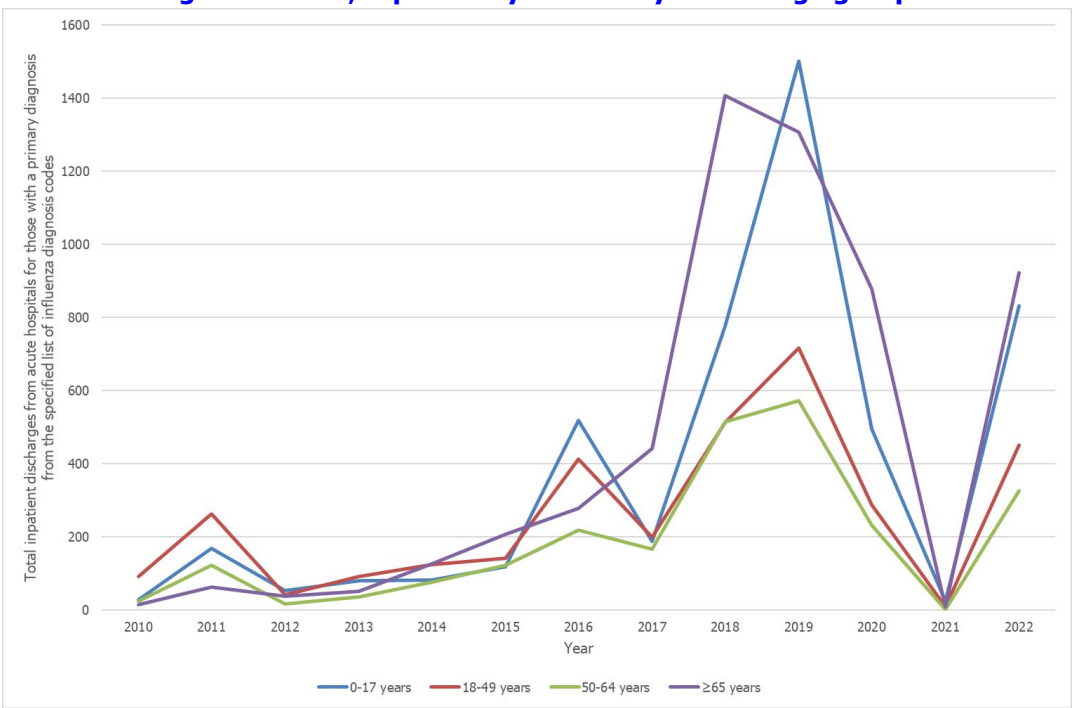
Figure 3.9 provides an overview of inpatient discharges with a primary diagnosis of influenza in those aged 65 years and older presented by five-year age band, and Figure 3.10 provides an overview of the same for the total population, reported by age band. On average, from 2010 to 2022 (excluding the years affected by COVID-19), those aged 65 years and older accounted for 34% (range: 9% to 44%) of all discharges per annum, for those with a primary diagnosis of influenza.

Figure 3.9 Total inpatient discharges from acute hospitals for those aged 65 years and older with a primary diagnosis from the specified list of influenza diagnosis codes, reported by calendar year and five-year age band



Source: Hospital In-Patient Enquiry System.

Figure 3.10 Total inpatient discharges from acute hospitals for those in the total population with a primary diagnosis from the specified list of influenza diagnosis codes, reported by calendar year and age group



Source: Hospital In-Patient Enquiry System.

Bed days for discharges with a primary diagnosis of influenza

Table 3.5 provides an overview of the mean annual hospital inpatient bed days and mean hospital LOS for those with a primary diagnosis of influenza, reported by age band. Considering the total population, there was evidence of substantial variability in the annual inpatient burden due to influenza as indicated by the wide range for each of the age bands. Patients aged 65 years and older accounted for 52% of all bed days with the highest mean annual number of bed days observed in this age group (3,853 (range: 88 to 14,914)). The mean hospital LOS increased with age ranging from three days in those aged 0 to 17 years, to nine days in those aged 65 years and older.

Considering those aged 65 years and older only, the mean annual bed days and mean hospital LOS increased with each increase in five-year age band. For example, the mean annual bed days was 635 days (range: 45 to 1,978) in those aged 65 to 69 years compared with 1,258 days (range: 94 to 4,883) in those aged 85 years and older. Again, there was evidence of substantial variability in the annual inpatient burden irrespective of the age band, with at least a three-fold difference between the minimum and maximum number of annual bed days recorded. Mean LOS generally increased with age, ranging from seven days in those aged 65 to 69 years to 12 days in those aged 85 years and older.

Table 3.5 Annual hospital inpatient bed days and length of stay per calendar year for those with a primary diagnosis of influenza (2010 to 2022) by age band

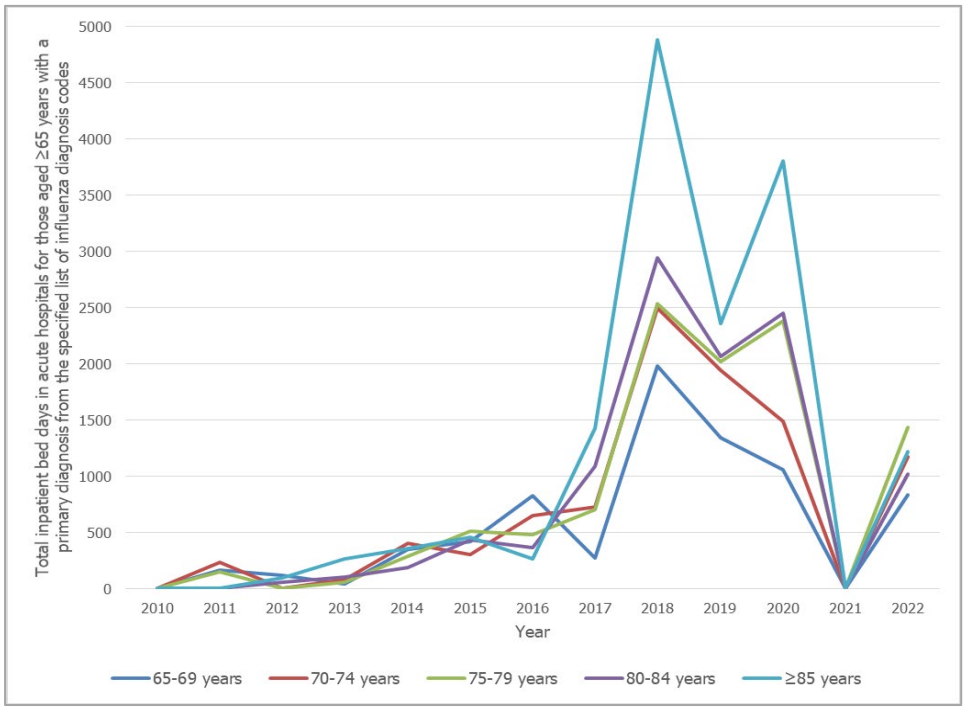
Age band (years)	Mean annual bed days (range)*	Mean LOS (days)*
0-17	1,240 (199-3,480)	3
18-49	1,071 (126-2,287)	4
50-64	1,243 (53-3,084)	6
65+	3,853 (88-14,914)	9
65-69	635 (45-1,978)	7
70-74	889 (79-2,495)	8
75-79	907 (55-2,534)	8
80-84	919 (59-2,943)	9
85+	1,258 (94-4,883)	12

Abbreviations: LOS – Length of stay.
Note: Hospital bed days associated with a primary diagnosis of influenza from the specified list of influenza diagnosis codes.
*Means exclude the years 2020 and 2021 (which are not considered representative due to the influence of COVID-19).
Source: Hospital In-Patient Enquiry System.

Figure 3.11 and Figure 3.12 depict the total annual bed days associated with influenza in those aged 65 years and older and for the total population, respectively. On average, from 2010 to 2022 (excluding the years affected by COVID-19), those

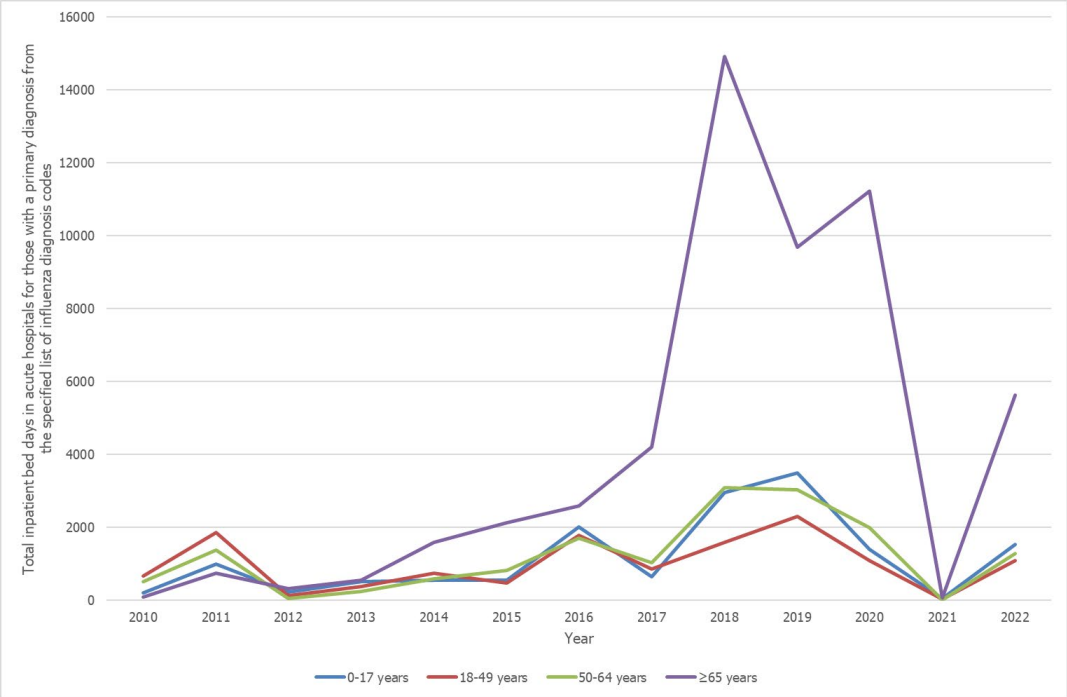
aged 65 years and older accounted for 52% (range: 6% to 66%) of all inpatient bed days per annum, for those with a primary diagnosis of influenza.

Figure 3.11 Total inpatient bed days in acute hospitals for those aged 65 years and older with a primary diagnosis from the specified list of influenza diagnosis codes, reported by calendar year and five-year age band



Source: Hospital In-Patient Enquiry System.

Figure 3.12 Total inpatient bed days in acute hospitals for those in the total population with a primary diagnosis from the specified list of influenza diagnosis codes, reported by calendar year and age group



Source: Hospital In-Patient Enquiry System.

Discharges with a primary diagnosis of influenza that included an intensive care unit stay and associated bed days

Table 3.6 provides an overview of the number of inpatient discharges that included an ICU stay for those aged 65 years and older with a primary diagnosis of influenza from 2010 to 2022. Reported also is the associated mean hospital LOS and total bed days for each year. These data were not available by five-year age band. In those aged 65 years and older, there were a total of 301 hospital discharges with an ICU stay, which equated to an annual average of 38 (range: 10 to 84) discharges with an ICU stay. There was considerable year-on-year variation, ranging from fewer than five discharges in 2010, 2012 and 2013 to 84 discharges in 2018 (note these data are reported according to calendar year not influenza season). The mean total bed days per year was 290 (range: 140 to 539). It should be noted that due to small numbers, the total inpatient LOS may have been heavily influenced by one or a small number of patients with a long LOS.

Table 3.6 Hospital discharges and associated mean length of stay and total bed days for those aged 65 years and older with a primary diagnosis of influenza that included an intensive care unit stay (2010 to 2022)

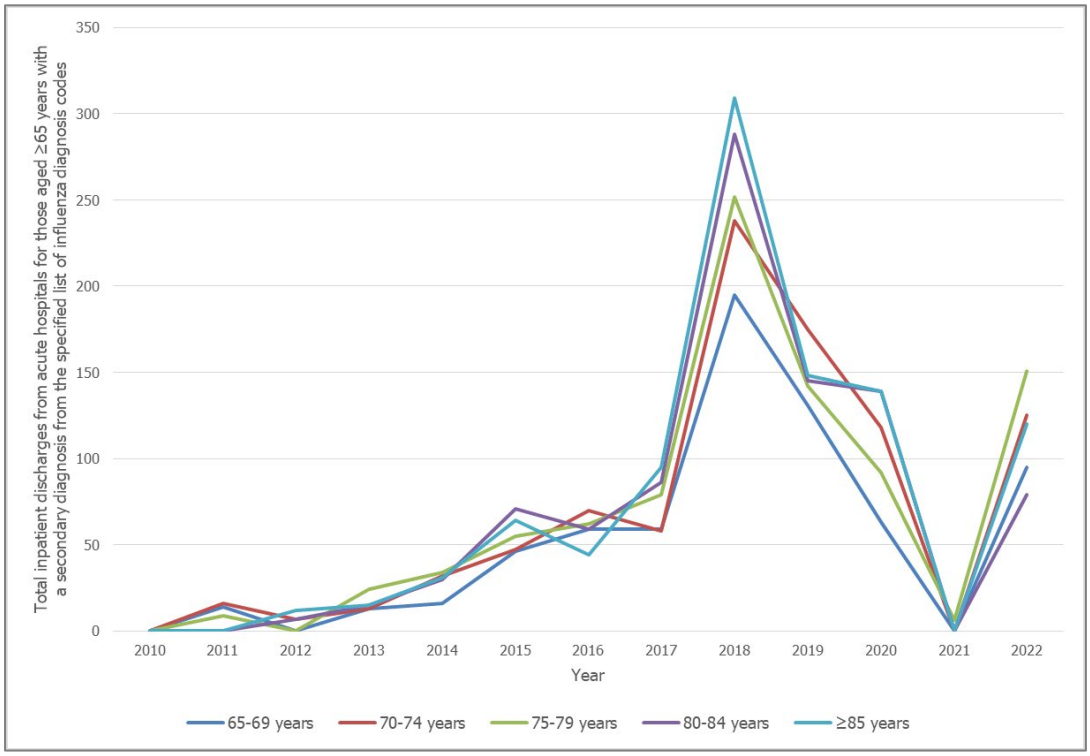
Year	Total discharges	Mean LOS	Total bed days
2010	-	-	-
2011	10	19	185
2012	-	-	-
2013	-	-	-
2014	10	14	140
2015	18	9	155
2016	37	11	418
2017	25	6	148
2018	84	6	504
2019	77	7	539
2020	63	7	441
2021	-	-	-
2022	40	6	228
Total*	**301**		**2,316**
Range*	10-84	6-19	140-539
Mean per year*	38		290
Mean bed days per patient*			8

Abbreviations: LOS – Length of stay.
Note: Hospital bed days associated with a primary diagnosis of influenza from the specified list of influenza diagnosis codes that included an intensive care unit stay. For reasons of confidentiality, counts are suppressed (and replaced with -) for cells where the number of discharges is ≤5; summary statistics are also suppressed.
*Figures reported exclude the years 2020 and 2021 (which are not considered representative due to the influence of COVID-19).
Source: Hospital In-Patient Enquiry System.

Discharges with a secondary diagnosis of influenza

Figure 3.13 provides an overview of inpatient discharges with a secondary diagnosis of influenza in those aged 65 years and older presented by five-year age band. A total of 3,862 discharges were reported from 2010 to 2022. This equated to an average of 351 (range: 16 to 1,282) discharges per year in this cohort; as per the primary diagnosis discharge data, the highest number of discharges with a secondary diagnosis of influenza was in 2018. Across all the years (and excluding 2020 and 2021), the mean number of discharges per annum was highest in those aged 85 years and older, followed by those aged 75 to 79 years. Data on the average hospital LOS in hospital for those with a secondary diagnosis of influenza were not available.

Figure 3.13 Total inpatient discharges from acute hospitals for those aged 65 years and older with a secondary diagnosis from the specified list of influenza diagnosis codes, reported by calendar year and five-year age band



Source: Hospital In-Patient Enquiry System.

3.4.3 Mortality in Ireland

Most patients experience uncomplicated illness secondary to influenza infection, but some develop severe disease which can be characterised by exacerbation of chronic medical conditions, acute respiratory distress syndrome, severe pneumonia, sepsis and potentially death.[107] Influenza-related mortality data were obtained from the HPSC.

Laboratory-confirmed influenza-related deaths per 100,000 for those aged 65 years and older for the winter and summer period are reported in Table 3.7. Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), influenza-related mortality rates for the winter period have varied (range: 1.7 to 24.9 per 100,000) in those aged 65 years and older. The corresponding influenza-related mortality rates for the summer period have been substantially lower (range: 0.0 to 0.5 per 100,000). In absolute numbers (and again excluding the seasons influenced by COVID-19), since the 2010-2011 season there has been a mean of 60 influenza-related deaths (range: 9 to 159) per annum in the winter period, and a mean of one death (range: 0 to 3) in the summer period. Based on these data, the case-fatality rate for laboratory-confirmed influenza in winter is approximately 4% per annum in those aged 65 years and older.

For the most recent season (2022-2023 season), data for which are provisional, the mortality rate for the winter period was 24.9 per 100,000 (n=159) versus 0.2 per 100,000 (n=1) for the summer period. The mortality rate reported for 2022-2023 was the highest observed mortality rate per 100,000 across all 13 seasons; this figure may increase further when data are finalised.

Table 3.7 Laboratory-confirmed influenza-related deaths per 100,000 from 2010-2011 to 2022-2023 in those aged 65 years and older in Ireland (winter and summer period)

Season (winter period)	Deaths		Season (summer period)	Notified cases	
	n	Rate per 100,000		n	Rate per 100,000
2010-2011	9	1.7	2011	0	0.0
2011-2012	9	1.7	2012	0	0.0
2012-2013	15	2.8	2013	0	0.0
2013-2014	36	6.7	2014	0	0.0
2014-2015	46	7.2	2015	0	0.0
2015-2016	41	6.4	2016	0	0.0
2016-2017	53	8.3	2017	1	0.2
2017-2018	157	24.6	2018	3	0.5
2018-2019	46	7.2	2019	3	0.5
2019-2020	88	13.8	2020	0	0.0
2020-2021	0	0.0	2021	0	0.0
2021-2022	13	2.0	2022	2	0.3
2022-2023	159	24.9	2023	1	0.2
Mean per annum*	**n=60**		**Mean per annum***	**n=1**	

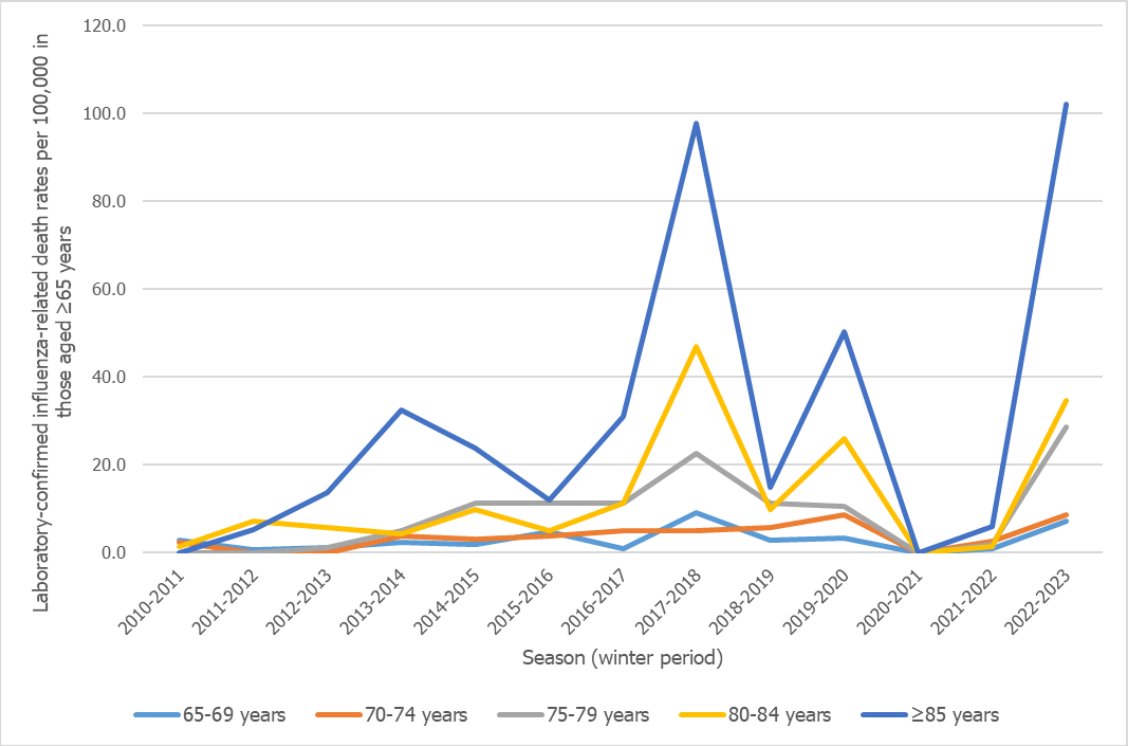
*Mean per annum excludes the seasons influenced by COVID-19 (2020-2021 and 2021-2022).
Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional.
Source: Health Protection Surveillance Centre.

Data on influenza-related mortality rates per 100,000 are presented in Figure 3.14 for those aged 65 years and older by five-year age band. From 2010-2011 to 2019-2020 there was a statistically significant increase in the rate of influenza-related deaths in those aged 70 years and older ($p<0.05$). In considering the winter period, and excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), the average number of laboratory-confirmed influenza-related deaths per annum was seven (range: 1 to 19) in those aged 65 to 69 years, seven (range: 0 to 14) in those aged 70 to 74 years, 12 (range: 0 to 33) in those aged 75 to 79 years, 12 (range: 1 to 38) in those aged 80 to 84 years and 23 (range: 0 to 69) in those aged 85 years and older. These data indicate substantial year-on-year variability, although typically higher mortality rates were observed with increasing age.

While data for the 2022-2023 season are provisional, the most recent data indicate a laboratory-confirmed influenza-related mortality rate of 7.1 per 100,000 (n=15) in those aged 65 to 69 years, 8.6 per 100,000 (n=14) in those aged 70 to 74 years, 28.6 per 100,000 (n=33) in those aged 75 to 79 years, 34.6 per 100,000 (n=28) in

those aged 80 to 84 years and 102.1 per 100,000 (n=69) in those aged 85 years and older.

Figure 3.14 Laboratory-confirmed influenza-related death rates per 100,000 from 2010-2011 to 2022-2023 in those aged 65 years and older, reported by five-year age band and season (winter period)

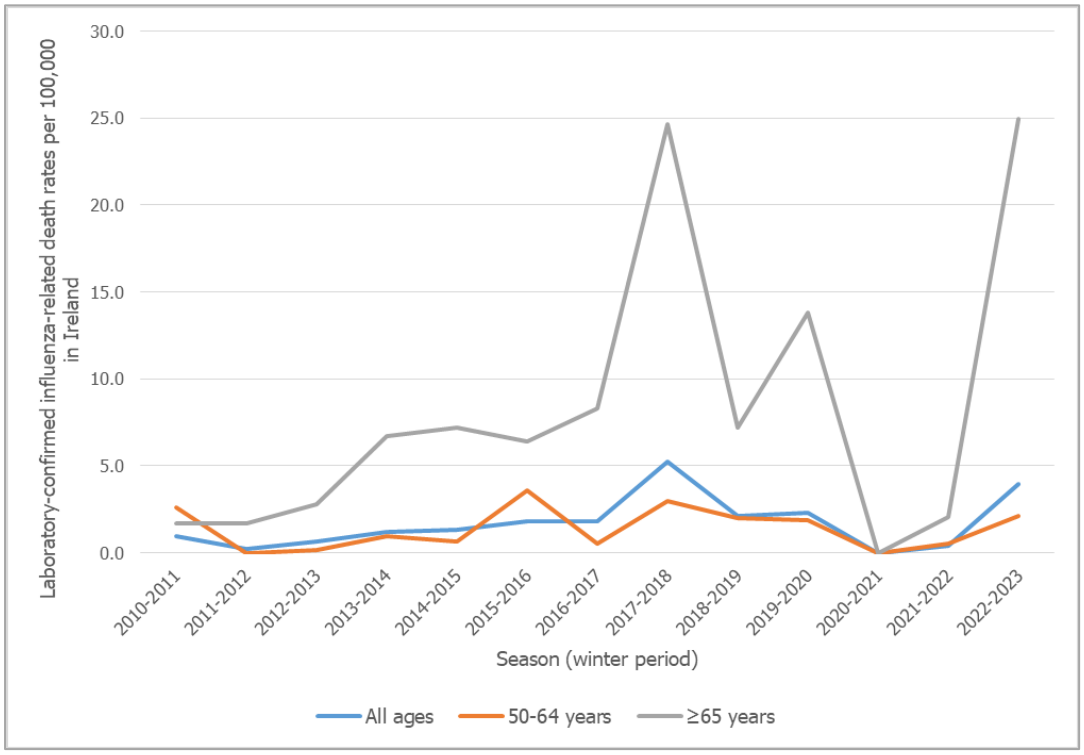


Note: Data for the 2021-2022 and 2022-2023 influenza seasons are provisional.
Source: Health Protection Surveillance Centre.

For context, Figure 3.15 provides an overview of the rates of laboratory-confirmed influenza-related deaths per winter period for the total population. These data are reported for the total population (that is, all ages), those aged 50 to 64 years and those aged 65 years and older. In general, influenza-related mortality rates in those aged 65 years and older are higher than in those aged 50 to 64 years (with the exception of the 2010-2011 influenza season). Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), on average per annum, 66% (range: 21% to 100%) of all influenza-related deaths occurred in those aged 65 years and older.

For the 2022-2023 season (data for which are provisional), the laboratory-confirmed influenza-related mortality rate was 3.9 per 100,000 (n=178) in the total population, 2.1 per 100,000 (n=17) in those aged 50 to 64 years, and 24.9 per 100,000 (n=159) in those aged 65 years and older; meaning, those aged 65 years and older accounted for 89% of all influenza-related deaths in the 2022-2023 season.

Figure 3.15 Laboratory-confirmed influenza-related death rates per 100,000 from 2010-2011 to 2022-2023 reported by age group and influenza season (winter period)



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

Excess mortality

Excess mortality is reported by EuroMOMO[108] as z-scores relative to baseline, that is, the expected number of deaths. The z-score provides the excess as the number of standard deviations from expected. A z-score of zero indicates that there is no difference from the expected number of deaths. A positive value indicates an excess of deaths while a negative value indicates mortality below that which is expected. Countries can be directly compared on the basis of z-scores, although consideration has to be given to how variance may differ across countries, particularly given the underlying population size. A z-score of:

- >0 and ≤2 indicates no excess mortality
- >2 and ≤4 indicates low excess mortality
- >4 and ≤7 indicates moderate excess mortality
- >7 and ≤10 indicates high excess mortality
- >10 and ≤15 indicates very high excess mortality

- >15 indicates extremely high excess mortality.

For this report, HPSC provided excess mortality data, extracted from the Weekly Mortality Report database, for the 2017-2018 season through to the 2023-2024 season. Data for earlier seasons were extracted from archived files and should be interpreted with caution. Therefore, in this report, we only report excess mortality for seasons 2017-2018 to 2023-2024, with the latter data truncated at 31 December 2023.

Figure 3.16 provides a summary of the z-scores for pneumonia- and influenza-related mortality in the total population, reported by season and week of the season. Pneumonia- and influenza-related mortality was observed in five of the six seasons for which data are complete, and typically occurred in the period between week 50 through to week 10. A high level of pneumonia- and influenza-related mortality was observed over a two-week period during each of the 2020-2021, 2021-2022 and 2022-2023 seasons, commencing at week 3 or 4. During the 2019-2020 season, a five-week period of moderate pneumonia- and influenza-related mortality was also observed at week 14; this coincided with the beginning of the COVID-19 pandemic in Ireland, that is, when restrictions came into force.

Figures 3.17 and 3.18 present excess all-cause mortality during the influenza season in the total population and specifically in those aged 65 years and older, respectively. Periods of excess all-cause mortality again were typically observed in the period between week 50 through to week 10. During the 2019-2020 season, there was also a seven-week period of excess all-cause mortality in all ages and in those aged 65 years and older. This started at week 13, with high levels of excess all-cause mortality observed during weeks 14 to 16. This excess all-cause mortality was likely due to COVID-19 and not influenza as there were no influenza positive non-sentinel specimens reported by the NVRL from 13 of 2020; at this time, testing for influenza was also reduced due to the COVID-19 pandemic response.[109]

Figure 3.16 Heat map showing z-scores for pneumonia- and influenza-related mortality from 2017-2018 to 2023-2024 in the total population, reported by season and week of the season

Week	40												52																				20
2017-2018	1.1	1.6	1.0	1.6	-1.6	-0.7	0.6	-1.2	0.6	0.6	1.0	1.5	3.9	4.6	5.0	4.7	2.2	3.0	1.5	1.3	0.0	2.6	2.7	1.8	-0.5	0.0	0.1	0.5	0.6	0.8	-0.8	-1.6	0.0
2018-2019	-0.5	-0.3	-0.8	-1.3	0.3	-1.6	1.1	-0.2	-0.8	-0.7	1.2	0.2	-0.1	1.2	1.6	0.6	1.5	1.1	0.2	0.5	-0.5	0.2	-0.6	-1.9	-1.6	-0.6	-1.0	-0.3	-0.7	-0.5	-0.1	1.3	1.8
2019-2020	-0.9	-0.1	-0.3	-1.2	0.5	-0.9	-0.2	0.6	-0.7	-1.1	1.6	3.1	2.8	4.4	2.3	1.5	1.4	0.1	-0.6	-0.2	0.1	-0.3	0.0	0.6	-0.3	1.7	4.6	6.8	6.3	4.3	4.1	1.9	0.4
2020-2021	0.8	0.0	-0.4	0.9	0.3	-1.2	-0.9	-1.5	-0.9	-0.9	-1.7	-1.7	-1.1	-0.3	2.5	6.9	7.5	7.2	6.1	4.5	3.4	2.4	-0.3	-1.2	-0.6	-0.7	-0.8	-1.4	-1.9	-0.8	-1.3	-1.5	-1.4	-2.4
2021-2022	1.4	1.5	2.1	1.0	2.2	1.0	0.7	1.3	1.3	0.8	-0.3	0.9	-0.2	2.5	6.9	7.5	7.2	6.1	4.5	3.4	2.4	-0.3	-1.2	-0.6	-0.7	-0.8	-1.4	-1.9	-0.8	-1.3	-1.5	-1.4	-2.4
2022-2023	0.6	-0.3	0.5	0.8	0.0	0.3	-0.1	0.6	1.5	-0.1	2.0	3.0	5.3	2.5	6.9	7.5	7.2	6.1	4.5	3.4	2.4	-0.3	-1.2	-0.6	-0.7	-0.8	-1.4	-1.9	-0.8	-1.3	-1.5	-1.4	-2.4
2023-2024	0.0	0.0	0.2	0.6	-0.3	-0.1	0.2	0.7	-0.4	0.0	-0.1	0.3	0.3																				

Note: Green – no excess mortality; yellow – low excess mortality; orange – moderate excess mortality; red – high excess mortality.
Source: Health Protection Surveillance Centre.

Figure 3.17 Heat map showing z-scores for all-cause excess mortality from 2017-2018 to 2023-2024 in the total population, reported by season and week of the season

Week	40												52																				20
2017-2018	0.4	0.6	0.9	1.4	-1.3	0.0	1.6	-0.1	-0.7	0.7	2.5	1.9	4.0	5.1	5.1	5.1	2.9	4.0	3.1	2.7	1.0	2.7	3.9	1.8	1.1	1.4	1.6	0.4	1.1	0.4	-1.1	-2.2	-0.7
2018-2019	-0.3	-0.6	0.5	-1.0	-0.7	1.0	-0.3	-0.4	-0.8	-0.2	0.4	-0.5	-0.3	0.5	1.8	0.1	2.0	1.8	1.7	1.3	-1.1	0.2	0.2	-0.6	-2.1	0.1	-1.1	0.6	-0.1	-0.9	0.3	1.8	-0.2
2019-2020	-0.6	0.1	0.0	0.5	0.8	-0.4	0.2	1.1	0.2	0.1	1.5	2.9	2.0	1.9	2.7	0.4	0.1	0.0	0.2	0.8	0.4	0.3	0.1	-0.1	0.9	2.7	7.3	9.3	8.1	5.5	2.9	2.1	1.1
2020-2021	0.6	0.2	0.0	0.3	1.0	-1.1	0.1	-1.7	-2.0	-0.6	-1.5	-1.0	-0.3	0.6	3.1	6.2	8.0	7.3	5.6	4.7	2.6	0.5	-0.6	-2.2	-2.2	-1.4	-0.6	-2.1	-0.6	-1.0	-0.8	0.5	-0.5	-1.3
2021-2022	-0.2	1.0	1.2	0.4	2.4	1.3	0.1	1.5	0.6	1.1	0.0	1.6	-0.3	3.1	6.2	8.0	7.3	5.6	4.7	2.6	0.5	-0.6	-2.2	-2.2	-1.4	-0.6	-2.1	-0.6	-1.0	-0.8	0.5	-0.5	-1.3
2022-2023	-0.8	0.5	-0.2	0.3	-0.4	-0.2	-0.4	-0.2	-0.1	0.8	2.1	4.5	5.3	3.1	6.2	8.0	7.3	5.6	4.7	2.6	0.5	-0.6	-2.2	-2.2	-1.4	-0.6	-2.1	-0.6	-1.0	-0.8	0.5	-0.5	-1.3
2023-2024	-0.5	-1.6	0.1	-0.5	-1.5	-1.0	-0.9	-0.3	-1.8	-0.4	-0.2	-0.8	-0.5																				

Note: Green – no excess mortality; yellow – low excess mortality; orange – moderate excess mortality; red – high excess mortality.
Source: Health Protection Surveillance Centre.

Figure 3.18 Heat map showing z-scores for all-cause excess mortality from 2017-2018 to 2023-2024 in those aged 65 years and older, reported by season and week of the season

Week	40												52																		20	
2017-2018	0.4	0.6	0.6	1.2	-1.4	-0.4	1.5	-1.0	-1.0	0.5	1.6	0.9	3.1	4.2	4.2	4.6	2.3	3.4	2.1	1.7	0.1	2.3	3.4	1.0	0.6	0.7	1.2	-0.2	1.2	0.4	-0.7	-2.0	-0.4	
2018-2019	-0.4	-0.2	1.2	-0.9	-0.8	0.9	-0.8	-1.4	-1.4	-1.3	-0.8	-1.0	-1.2	0.0	0.4	-0.9	0.8	1.1	0.6	0.4	-1.1	-1.1	-0.1	-1.2	-2.4	-0.5	-1.3	0.7	-0.3	-1.2	-0.2	1.7	-0.3	
2019-2020	-0.3	0.0	-0.3	0.8	1.1	-0.1	0.1	0.8	-0.1	-0.7	0.6	2.0	1.8	2.1	2.2	0.0	-0.5	-0.4	0.0	0.2	-0.2	-0.2	0.1	-0.1	0.6	2.3	7.4	9.5	9.2	5.6	3.7	2.3	1.1	
2020-2021	1.1	0.0	0.4	-0.2	0.8	-1.0	-0.2	-1.8	-1.6	-1.0	-1.8	-1.7	-0.5	0.1	2.4	5.9	7.7	7.4	5.3	4.2	1.9	-0.2	-0.9	-2.2	-2.2	-1.7	-1.3	-1.9	-1.0	-1.3	-0.4	0.4	0.0	-1.2
2021-2022	0.4	1.5	1.3	-0.1	1.7	0.9	0.2	1.3	0.6	0.9	-0.2	1.3	-1.0	2.4	5.9	7.7	7.4	5.3	4.2	1.9	-0.2	-0.9	-2.2	-2.2	-1.7	-1.3	-1.9	-1.0	-1.3	-0.4	0.4	0.0	-1.2	
2022-2023	-0.2	1.0	0.6	0.7	0.1	0.2	0.2	0.2	0.6	0.8	2.7	4.4	5.4	2.4	5.9	7.7	7.4	5.3	4.2	1.9	-0.2	-0.9	-2.2	-2.2	-1.7	-1.3	-1.9	-1.0	-1.3	-0.4	0.4	0.0	-1.2	
2023-2024	0.2	-0.8	0.4	-0.5	-1.2	-0.8	-0.6	0.0	-1.6	0.1	-0.1	-0.7	-0.3																					

Note: Green – no excess mortality; yellow – low excess mortality; orange – moderate excess mortality; red – high excess mortality.
Source: Health Protection Surveillance Centre.

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

The joint ECDC–WHO Regional Office reports on influenza activity in the 54 countries and areas with routine influenza surveillance systems in the WHO European Region. Through the HPSC, Ireland contributes to these data and reports on laboratory-confirmed influenza-positive cases in ICU and or other hospital wards.[110] However, assessing the influenza burden of disease is not straightforward; diagnosis is rarely confirmed by laboratory testing, a number of respiratory viruses produce similar symptoms, not all those with the virus attend a doctor and much of the burden is due to complications not necessarily directly attributed to influenza as the underlying cause.[111]

A Spanish study comprising data from ten influenza epidemic seasons (2008/2009-2017/2018), excluding data for H1N1pdm09 pandemic (2009/10), estimated the clinical and economic burden of severe influenza measured through hospitalisations and deaths.[112] The estimated mean annual number of hospitalisations across all age groups (inclusive of those with comorbidities) was 28.1 cases per 100,000 people, with hospitalisation rates differing by age group. Patients aged 65 years and older contributed to 56.7% of hospitalisations with a diagnosis of influenza (mean 88.2 cases per 100,000 over nine seasons, reaching 289.3 cases per 100,000 in 2017-2018). Patients aged 65 years and older with comorbidities accounted for 40.1% of hospitalisations, and those aged 65 years and older without comorbidities accounted for 16.5% of hospitalisations. The mean hospital LOS differed by age group and depended on the presence or absence of comorbidities. Across all seasons, the mean hospital LOS was 9.8 days (range: 7.9 to 11.1 days) in those aged 65 years and older.[112] In those aged 65 years and older, the mean hospital LOS was higher in those with comorbidities compared with those without comorbidities at 10.1 days (range: 8.0 to 11.3) versus 8.8 days (range: 6.0 to 11.3).[112]

A 2022 study sought to estimate the epidemiological and economic burden of severe influenza over eight seasons (2010-2018) in France.[113] Analysis of hospitalisation data for 2010-2018 and mortality data for 2010-2015 were stratified by age group. Results indicated that the annual average rate of hospitalisation was 28 per 100,000. The majority of influenza-related hospitalisations (64%) occurred in the youngest (that is, those aged 0 to 4 years) and oldest (that is, those aged 65 years and older) age groups. Across the whole study period, median hospital stay was threefold higher for those aged 85 years and older (median: 10 days, range: 9 to 10) than for those aged 0 to 4 years (median: 3 days, range 3 to 3). The proportion of intensive care unit transfer was 23.1% for those aged 50 to 64 years. Those aged 65 years and older accounted for 80% of in-hospital deaths due to influenza.[113]

Pre-COVID-19 pandemic surveillance reports for the UK show variability in terms of the severity of influenza seasons. For example, the 2018-2019 influenza season showed low to moderate levels of influenza activity in the community. With the exception of Northern Ireland, the highest levels of activity associated with primary care consultations were observed in those aged less than 64 years.[114] Conversely, the 2017-2018 season showed moderate to high levels of influenza activity in the UK, with co-circulation of influenza B and influenza A(H3).[83] The majority of this burden was observed in older adults, with repeated outbreaks in long-term care facilities and high rates of hospitalisations and ICU admissions. During this season, activity associated with primary care consultations in England peaked in those aged 45 to 64 years (74.4 per 100,000) and in those aged 65 to 74 years (58.4 per 100,000). In Scotland, the highest levels of activity were seen in those aged 75 years and older (219.8 per 100,000) and those aged 45 to 64 years (159.0 per 100,000). In Wales, the highest levels of activity were seen in those aged 45 to 64 years (111.6 per 100,000) and those aged 15 to 44 years (70.6 per 100,000). While in Northern Ireland, the highest levels of activity were seen in those aged 45 to 64 years (89.9 per 100,000) and those aged 65 to 74 years (76.7 per 100,000).[83]

3.5 Vaccination against influenza

Vaccination can offer protection against seasonal influenza by preventing infection and or reducing its impact, as well as preventing onward transmission to others. Annual vaccination is recommended because of waning immunity and also due to the fact that influenza strains can change each year. Vaccine effectiveness varies from year to year; this is due to a range of factors such as, an individual's age or health status, virus types and subtypes in circulation, and the degree of matching between the circulating strain and the vaccine content.[9]

3.5.1 Uptake of influenza vaccination in Ireland

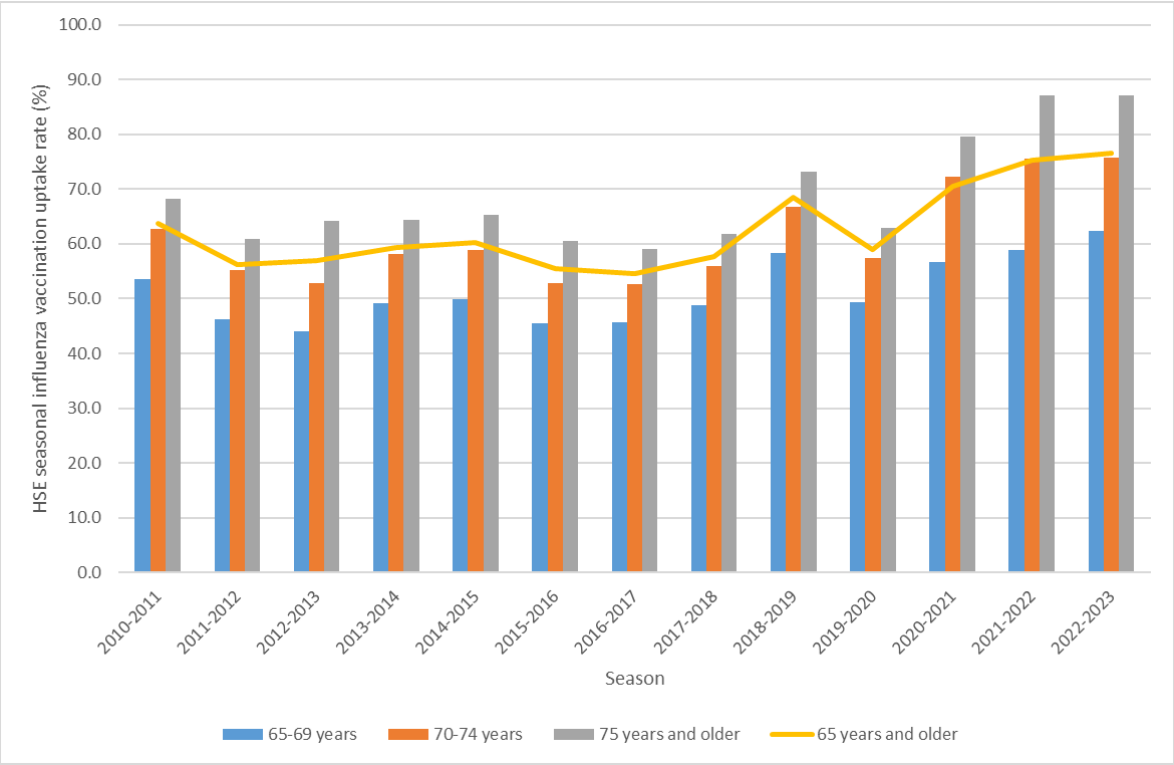
Historical uptake data for influenza vaccination in Ireland were obtained from the HPSC. These figures reflect the administration of influenza vaccines reimbursed through the HSE Seasonal Influenza Vaccination Programme and include data across all settings: GP practices, community pharmacies, long-term care facilities (LTCFs) and hospitals. The figures do not include influenza vaccinations provided through occupational health schemes, though it is anticipated that the majority of those aged 65 years and older will avail of influenza vaccination through the HSE's programme rather than through occupational health schemes.

Figure 3.19 reports the seasonal influenza vaccination uptake for those aged 65 years and older, reported by age group and season, from the 2010-2011 to the 2022-2023 season. With the exception of the 2021-2022 season when an aIIV was

offered to those aged 65 years and older, the HSE Seasonal Influenza Vaccination Programme for adults was limited to standard IIVs over this time period. Excluding the years influenced by COVID-19, the average seasonal influenza vaccination uptake was 60.7% (range: 54.5% to 76.5%) in those aged 65 years and older. When disaggregated by five-year age band, uptake was consistently higher in older age groups with an average uptake of 50.2% (range: 44.1% to 62.3%) in those aged 65 to 69 years, 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. Currently, there are nine Community Healthcare Organisations (CHOs) responsible for the delivery of primary and community-based services in Ireland. Variation in vaccine uptake (in those aged 65 years and older) has been observed between CHOs, ranging, for example, from 64.6% in CHO area 1 to 83.7% in CHO area 6 in the 2022-2023 season.[115] For the 2022-2023 season, the overall seasonal influenza vaccination uptake in those aged 65 years and older was 76.5% (n=568,511). This was the first season in which the vaccination of healthcare workers and LTCF residents was also accounted for; this addition may account for some of the increased uptake in the 2022-2023 influenza season relative to the preceding years.

For context, it is noted that uptake is considerably higher in those aged 65 years and older compared with the rest of the population. For example, in 2022-2023, the seasonal vaccination uptake was 15.3% in those aged 2 to 17 years, 11.3% in those aged 18 to 49 years and 30.0% in those aged 50 to 64 years.[115]

Figure 3.19 Seasonal influenza vaccination uptake 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.

As described in Chapter 2, eligible individuals living in the community can access the influenza vaccine either through their GP or their community pharmacy. For individuals residing in LTCFs, the vaccine may be administered by mobile HSE vaccination teams who attend the settings to deliver COVID-19 and influenza vaccines to residents. The cost of administering the vaccine to one individual in the community during the 2022-2023 influenza season was approximately €25; this included the fee for administering the vaccine (€15) and the additional amount payable for every 10 unique patients vaccinated (GP and pharmacy costings). GPs and pharmacists are eligible for a payment of €100 for every 10 unique patients to whom the QIV vaccine is administered.[116] While the cost of vaccine administration in LTCFs by HSE vaccination teams will likely differ, these individuals represent a minority of the total population aged 65 years and older. Assuming that the cost of vaccine administration is the same for all individuals, based on the published administration fees, it is estimated that the cost of vaccine administration for 568,511 adults aged 65 years and older (based on the 76.5% coverage rate observed during the 2022-2023 season) was approximately €14.21 million.

Influenza vaccines are marketed as pre-filled syringes containing a single dose and are subject to 23% VAT. Vaccine acquisition is typically based on a competitive tender process with the final price commercially confidential. The composition of

influenza vaccines change every season; as such, vaccines from one season cannot be carried over and used the following season. Contracted prices for influenza vaccines may also include arrangements for return of unused stock given that the composition of these vaccines is season specific. Based on a vaccine dose cost of €10 for the standard QIV and a 76.5% coverage rate, the total cost of vaccinating those aged 65 years and older (including the administration fees) during the 2022-2023 season was approximately €21.2 million. However, this could have ranged from €17.7 million (based on a vaccine dose cost of €5) to €24.7 million (based on a vaccine dose cost of €15), depending on the vaccine dose cost.

3.5.2 Uptake of influenza vaccination in EU/EEA countries and the UK

The ECDC have published annual surveys on seasonal influenza immunisation policies and vaccination coverage in EU/EEA Member States with a view to monitoring compliance with the 2009 Council recommendation to achieve an EU goal of 75% vaccine coverage in older age and risk groups.[117] The most recent report, based on survey data gathered in January 2018, indicated differences in vaccination coverage across countries.[118] These data were reported separately for healthcare workers, those with chronic medical conditions, pregnant women, residents of LTCFs and older age groups. Of note, older age was variably defined as age ≥55, ≥59, ≥60 or ≥65 years as per Member States recommendations. Given that uptake increases with age, countries adopting a lower definition for older age may be anticipated to have lower uptake. 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.[118]

More recent data published in the UK (2020-2021 season) reports that in England, the influenza vaccination uptake was 80.9% in those aged 65 years and older (compared with 72.4% in 2019-2020 season and 72.0% in 2018-2019 season).[119] For the same age group and season, the influenza vaccination uptake was 79.6% in Scotland (compared with 74% in the previous two seasons), 76.5% in Wales (compared with 69.4% in 2019-2020 season and 68.3% in 2018-2019 season) and 79.1% in Northern Ireland (compared with 74.8% in 2019-2020 season and 70% in 2018-2019 season).[114, 120]

3.6 Treatment for influenza

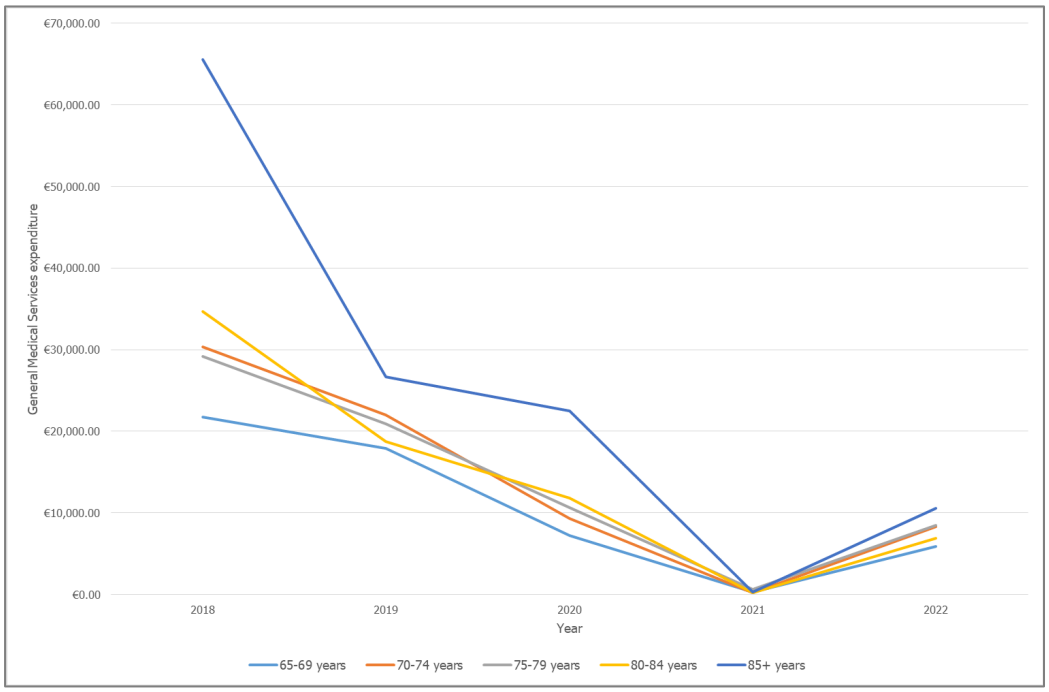
Seasonal influenza is characterised by respiratory and systemic symptoms including fever, malaise, myalgia, headache, sore throat and nasal congestion.[22] Gastrointestinal symptoms such as nausea, vomiting and diarrhoea are also common. In most healthy individuals, seasonal influenza is self-limiting and

symptoms typically resolve in three to seven days. Treatment for these individuals consists of antipyretics, adequate fluid intake and rest. However, certain individuals have an increased risk of severe disease and may require hospitalisation and or treatment with antivirals.[22] These high-risk groups include those with underlying medical conditions (such as chronic respiratory disease, chronic heart disease and diabetes), infants and young children, pregnant women and those aged 65 years and older.[23]

In Ireland, the Primary Care Reimbursement Service (PCRS) collate data on medications dispensed by community pharmacists through a range of publicly-funded community drug schemes (for example, General Medical Service (GMS), Drugs Payment Scheme (DPS) and Long-Term Illness (LTI)). Eligibility and co-payments for these schemes differ. For those who do not qualify for any of these schemes, the full cost of influenza treatments in the community must be paid for out-of-pocket. The PCRS data do not capture where the prescription is paid for privately, nor do they include claims which are under the DPS monthly threshold amount. PCRS data do not capture information relating to diagnoses or indications for the medicines reimbursed.

Oseltamivir and zanamivir are two antiviral agents indicated for infections caused by influenza. PCRS expenditure data relating to J05AH02 (oseltamivir) were obtained for the years 2018 to 2022. Expenditure varied substantially by year. Mean annual GMS expenditure on oseltamivir in those aged 65 years and older was €78,145 ranging from €1,551 in 2021 to €181,446 in 2018. The highest annual expenditure was consistently in those aged 85 years and older (range: €294 to €65,538; mean: €25,104) (see Figure 3.20).

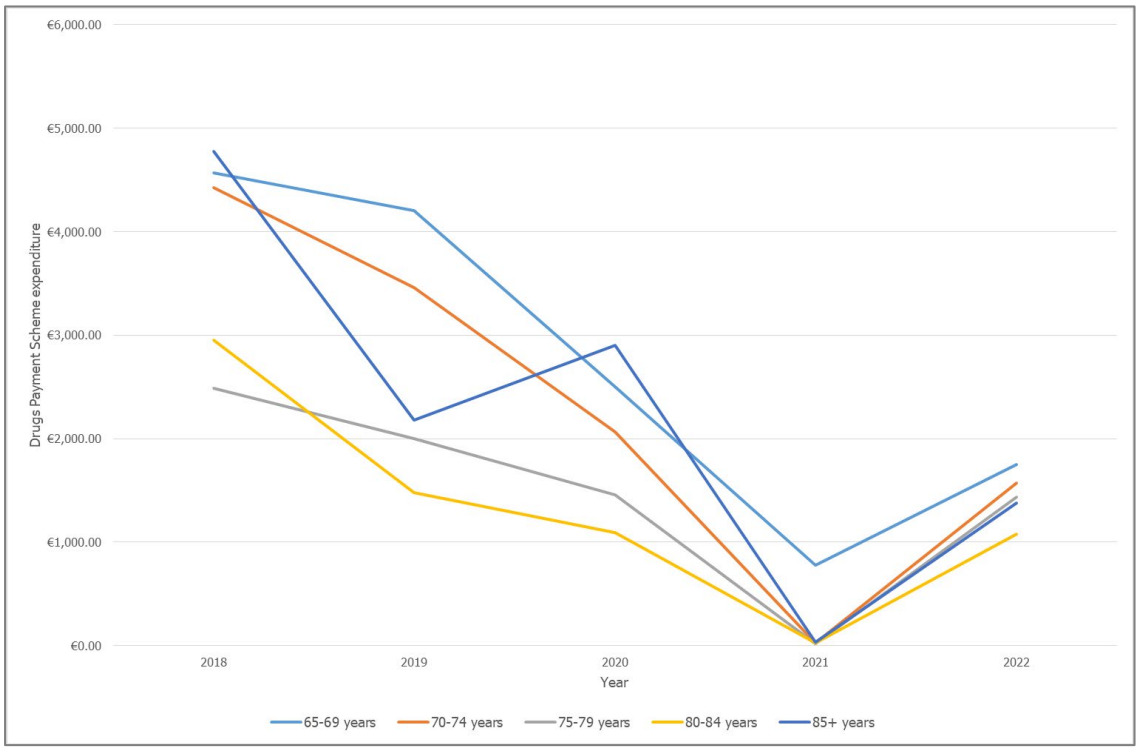
Figure 3.20 General Medical Services expenditure on oseltamivir from 2018 to 2022 for those aged 65 years and older, reported by age group and year



Source: Primary Care Reimbursement Service.

Annual expenditure on oseltamivir through the DPS ranged from €881 in 2021 to €19,215 in 2018 (mean: €10,131) in those aged 65 years and older. The highest annual expenditure was in those aged 65 to 69 years (range: €779 to €4,570; mean: €2,761) (see Figure 3.21).

Figure 3.21 Drugs Payment Scheme expenditure on oseltamivir from 2018 to 2022 for those aged 65 years and older, reported by age group and year



Source: Primary Care Reimbursement Service.

LTI expenditure on oseltamivir was only reported in 2018. This amounted to €26 in those aged 65 to 69 years and €81 in those aged 75 to 79 years (total expenditure in 2018 was €107).

PCRS data were not available for zanamivir as it is not reimbursable under any community drug scheme.[121]

3.7 Economic burden of influenza

HIPE data are used to create Diagnosis Related Groups (DRGs) to inform Activity Based Funding,[122] which is a funding model for hospital care for inpatient and day-case services.[123] Using this model, a specified price is paid to each hospital for each weighted unit of inpatient and day-case work undertaken. DRGs are used to classify patient hospital encounters into a manageable number of groups which can be used to describe the mix of cases or activity being carried out by a hospital.[99] DRGs group together cases which are clinically similar and expected to consume a similar amount of resources. Currently, Ireland is using the ICD-10-AM/ACHI/ACS 10th edition, otherwise known as the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification, Australian Classification of Health Interventions, Australian Coding Standards (referred to as

ICD-10-AM for simplicity). The DRG classification uses data coded using the ICD-10-AM classification system along with other routinely collected data to classify episodes of acute care. DRGs provide a clinically meaningful way of relating the number and types of acute admitted patients to the resources required by the hospital.[124]

For this assessment, data for the following DRGs (relating to calendar years 2018, 2019 and 2022) were used:

- D63A: Otitis media and upper respiratory infection – major complexity
- D63B: Otitis media and upper respiratory infection – minor complexity
- E62A: Respiratory infection/inflammation – major complexity
- E62B: Respiratory infection/inflammation – minor complexity.

Table 3.8 provides an overview of the mean number of inpatient discharges (mean number of bed days and associated costs) per annum from acute hospitals for those aged 65 years and older, with a principal diagnosis from the specified list of influenza diagnosis codes. These data are reported by DRG. Data were not available by five-year age band and instead are reported for the following age bands: 65 to 74 years, 75 to 84 years and 85 years and older.

The most common DRG was D63A (Otitis media and upper respiratory infection – major complexity) which contributed 75% of the total discharges, followed by E62A (Respiratory infection/inflammation – major complexity) which contributed 12% of the total discharges. DRG E62B (Respiratory infection/inflammation – minor complexity) contributed 4% of discharges. On average, 60% of discharges and 69% of bed days accrued to those aged 75 years and older.

Costs associated with each DRG were approximated using the ABF 2023 Admitted Patient Price List.[125]

In total, across the included DRGs, the cost of care associated with seasonal influenza in acute hospitals was estimated at approximately €6.03 million per annum. However, it is acknowledged that this is likely an underestimate as not all influenza cases are tested and some discharges may not be coded.

Table 3.8 Mean number of inpatient discharges (mean number of bed days and associated costs) per annum from acute hospitals for those aged 65 years and older, with a principal diagnosis from the specified list of influenza diagnosis codes, reported by Diagnosis Related Group and age band

		D63A: Otitis media and upper respiratory infection - major complexity	D63B: Otitis media and upper respiratory infection - minor complexity	E62A: Respiratory infection/ inflammation - major complexity	E62B: Respiratory infection/ inflammation - minor complexity	Total
Mean inpatient discharges (mean bed days) per annum*	65-74 years	360 (2,161)	48 (116)	45 (514)	21 (93)	474 (2,884)
	75-84 years	371 (2,762)	26 (81)	59 (827)	21 (118)	477 (3,788)
	≥85 years	177 (1,841)	9 (41)	39 (665)	13 (93)	238 (2,640)
Mean total discharges per annum*		908	83	143	55	1,189
Total cost per annum~ (€)		4,335,700	196,378	1,277,133	218,460	6,027,671

*Based on data from 2018, 2019 and 2022.
~Based on the ABF 2023 Admitted Patient Price List.
Source: Hospital In-Patient Enquiry System.

Influenza places a large economic burden on society and healthcare systems internationally. In considering the economic burden associated with influenza, both direct and indirect costs are relevant.[126] Direct costs include those related to providing care for the patient — for example, primary care visits, medication costs and hospitalisation costs.[127] Indirect costs include productivity losses due to illness, disability related to consequential conditions of the disease, or premature death.[127] The level of population immunity and the characteristics of the circulating strain of the virus present variations in the year-to-year burden of disease, making it difficult to estimate economic impact and the annual number of deaths.[15] Management of influenza 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 influenza in secondary care is often a challenge due to diagnostic uncertainty. For example, the symptoms of influenza are non-specific and not all patients will have specimens collected and tested. Moreover, some patients may acquire influenza during their inpatient stay rather than influenza being the cause of admission, although this is partly accounted for using the primary diagnosis code.[128]

Notwithstanding these challenges, many studies have estimated the economic burden of influenza. A UK study has described the direct medical costs of secondary care influenza-related admissions in England during the 2017-2018 and 2018-2019 influenza seasons.[128] A total of 46,215 influenza-related hospital admissions were recorded for 41,730 individual patients for the 2017-2018 influenza season. This fell to 39,670 influenza-related hospital admissions for 35,415 patients in the 2018-2019 influenza season. The results showed that (for the 2017-2018 influenza season) the average hospital LOS (12.55 days) and cost (approximately £3,500) per influenza-related admission were highest in those aged 75 years and older, followed by those aged 65 to 74 years (average hospital LOS: 9.08 days, cost: approximately £3,000). The in-hospital mortality rate also increased with age, from 2.16% in those aged 65 years and under to 11.02% in those aged 75 years and older. Similar results were reported for the 2018-2019 influenza season with the average hospital LOS (12.55 days) and cost (approximately £3,700) per influenza-related admission being highest in those aged 75 years and older, followed by those aged 65 to 74 years (average hospital LOS: 9.04 days, cost: approximately £3,100). The proportion of in-hospital deaths for the same season was 1.83% in those aged 65 years and under, and 11.18% in those aged 75 years and older.[128]

3.8 Discussion

This chapter describes the epidemiology of seasonal influenza and the burden of disease in Ireland, EU/EEA countries and the UK among adults aged 65 years and older. In summary, influenza surveillance data for Ireland show that, excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), there has been

substantial year-on-year variability in the seasonal burden associated with influenza in those aged 65 years and older over the 13-year period since 2010-2011. Specifically, considering data for the winter period, there has been variation in the annual number of notified influenza cases (mean=1,656, range: 134 to 4,581), laboratory-confirmed influenza-related hospital admissions (mean=797, range: 36 to 2,245), hospital admissions with an ICU stay (mean=43, range: 5 to 108) and influenza-related deaths (mean=60, range: 9 to 159). Based on these data, the case-fatality rate for laboratory-confirmed influenza in winter is approximately 4% per annum in those aged 65 years and older.

The proportion of the total burden associated with seasonal influenza occurring in those aged 65 years and older has also varied over time. This was evident for data relating to notified influenza cases (range: 6% to 42%), laboratory-confirmed influenza-related hospital admissions (range: 10% to 49%), hospital admissions with an ICU stay (range: 15% to 59%) and mortality (range: 21% to 100%). However, in acknowledging this variability, the disproportionate burden associated with influenza in those aged 65 years and older particularly on secondary care services must be highlighted relative to their proportion of the total population. On average, 38% of laboratory-confirmed influenza-related hospital admissions per annum occurred in those aged 65 years and older, and while the proportion of the population aged 65 years and older has increased over time, they only represented 11.7% of the population in 2011[100] increasing to 15.1% in 2022.[102]

The population aged 65 years and older are not homogenous. When data for this group are disaggregated by five-year age band, in general, the burden of influenza increases with increasing age. For example, rates of notified influenza cases, influenza-related hospital admissions and influenza-related deaths were highest in those aged 85 years and older. This trend was not observed for influenza-related hospital admissions that included an ICU stay where the burden was highest in those aged 75 to 79 years and lowest in those aged 80 to 84 years. This may reflect ICU admission policies rather than differences in influenza severity.[129]

In general, there is a trend of increased incidence of notified influenza cases, influenza-related hospital admissions and influenza-related mortality over time. As noted, the proportion of the population aged 65 years and older has increased over time, from 11.7% in 2011[100] to 15.1% in 2022.[102] This proportion is set to continue to increase, with population projections predicting that the proportion of the total population aged 65 years and older will reach 17.3% in 2028 and 19.0% in 2033.[130] Moreover, the population group aged 80 years and older (who, in this assessment, accounted for 38% of hospital discharges and 47% of bed days per year with a primary diagnosis of influenza) 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.[131] This will likely have a significant knock-on effect on the healthcare system in terms of the healthcare utilisation associated with influenza and other vaccine-preventable diseases.

It is unclear whether the increased incidence of notified cases is because incidence of influenza is genuinely higher due to greater transmission (through, for example, more mixing and or changing virus characteristics), or less immunity (for example, due to a more frail population or reduced vaccine effectiveness). If the incidence of influenza is genuinely increasing over time, it would be important to understand the underlying causal factors as this should inform the policy response. In a survey of respiratory virus testing capacity and practices in acute hospital settings in Ireland (published in 2023),[132] it was 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. Assuming that the increase in capacity was driven by 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 influenza 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. Additionally, the 2023 survey[132] showed that 93% of laboratories reported testing specimens from hospital inpatients and ICU patients, making these the most common source of specimens; only 30% of laboratory-tested specimens were submitted from primary care practices. As such, the true burden of influenza in primary care is likely much higher than that reported.

In Europe, where influenza surveillance is jointly coordinated by the WHO Regional Office for Europe and the ECDC, seasonal influenza viruses are estimated to cause up to 50 million symptomatic infections each year, with an estimated 15,000 to 70,000 deaths of European citizens as a result of influenza-associated causes.[15] Additionally, patients infected with influenza can experience co-infection with other pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and respiratory syncytial virus (RSV) which can further complicate the clinical picture and contribute to increased morbidity and mortality. The US Centers for Disease Control and Prevention (CDC) warned of a possible "Tripledemic" of influenza, SARS-CoV-2 and RSV in the 2023-2024 season, issuing advice on how to protect oneself.[133] While acknowledging this risk, to date in Ireland, in those aged 65 years and older, reported rates of co-infection among notified cases have been low.

International data from a systematic review of the clinical burden of influenza in those aged 65 years and older substantiate the findings relating to the burden of influenza in this cohort in Ireland. This systematic review reported a disproportionate burden in those at higher risk of severe disease — that is, those aged 65 years and

older, living in long-term care facilities, with underlying medical conditions.[134] Specifically, the risk of influenza-related hospitalisation was higher in those aged 65 years and older with existing long-term conditions such as cardiovascular diseases (CVD), respiratory diseases, immunosuppressive conditions and diabetes mellitus compared with those without these conditions.[134] As described in Section 3.3.4, a study conducted in Spain estimated the clinical and economic burden of severe influenza through hospitalisations and deaths over the course of ten influenza seasons. Patients aged 65 years and older contributed to the majority (56.7%) of hospitalisations with a diagnosis of influenza. Moreover, patients with comorbidities accounted for 59.0% of hospitalisations, of which 68.0% were aged 65 years and older.[112]

The substantial burden associated with influenza in those aged 65 years and older in Ireland is in the context of an existing HSE Seasonal Influenza Vaccination Programme that offers a (free at the point of delivery) standard QIV to this cohort. For the 2022-2023 season, data show an influenza vaccination coverage rate of 76.5% in this cohort. While an annual, well-matched seasonal influenza vaccine can offer protection to the individual receiving the vaccine, and against onward transmission, a number of factors influence its effectiveness. These include waning immunity, antigenic drift and an individual's age or health status.[9] Data relating to the effectiveness and safety of the enhanced inactivated influenza vaccines will be assessed in detail in Chapter 4.

In addition to vaccine effectiveness, vaccination coverage rates also influence the level of protection garnered. Vaccination is voluntary and typically is only systematically offered to selected groups (for example, based on clinical care plans for those identified to be at elevated risk of severe disease or through employer occupational health schemes for healthcare workers). Therefore, programmes often rely on individuals seeking vaccination, knowing it is available and being encouraged to avail of it. However, given that for several years in Ireland, all individuals aged 65 years and older have been eligible for free at the point of delivery vaccination based on their age through the HSE Seasonal Influenza Vaccination Programme, it is less likely that they are unaware of its availability. Vaccination uptake data relating to the administration of influenza vaccines reimbursed through the HSE Seasonal Influenza Vaccination Programme indicate that the average seasonal influenza vaccination uptake since 2010-2011 in those aged 65 years and older was 60.7% (range: 54.5% to 76.5%) with evidence that uptake increases with age. Variation in vaccine uptake was observed between CHO areas which may be indicative of local-level barriers to access and or highlight opportunities for targeted initiatives to improve uptake. At a programme level, higher uptake in the 2022-2023 season (uptake 76.5%) may reflect the fact that the data were more complete than in preceding years as this was the first season in which data relating to the vaccination of healthcare workers

and long-term care facility residents were included. For those aged 65 years and older, it is noted that with the exception of the 2021-2022 season when the adjuvanted IIV was offered, the HSE Seasonal Influenza Vaccination Programme (for the period 2010-2011 to 2022-2023) was based on a standard IIV. While this change to an enhanced vaccine could have led to increased uptake given expectations of improved health outcomes associated with a potentially more effective vaccine, it is also possible that uptake in a subsequent season could be negatively impacted given the increased risk of local and systemic adverse events with adjuvanted IIVs. In the absence of patient-level data and given differences in the completeness of the data, as well as uncertainty regarding the impact of COVID-19 during those years on individuals' attitudes towards vaccination and perceptions of risk, it is not possible to determine the impact of the 2021-2022 vaccine policy change on uptake in Ireland.

As highlighted in Section 2.5, internationally, a number of countries fund enhanced IIVs as part of their immunisation programmes. While a systematic review was not undertaken to identify the impact of influenza vaccine type on uptake, it is noted that vaccine uptake in the UK has remained consistently high (exceeding the WHO target of 75%) despite changes in vaccine policy, which include the funding of enhanced vaccines for those aged 65 years and older. Specifically, adjuvanted IIVs were first offered by the UK immunisation programme for the 2018-2019 season with the programme subsequently expanded to also include cell-based and recombinant IIVs.[135] For the 2022-2023 season, overall the uptake was 79.9% in those aged 65 years and older; where data on vaccine type were available, 94.4% of the uptake related to the adjuvanted IIV.[136] This would suggest that at a population-level, switching to an enhanced vaccine did not impact uptake in the UK.

The HSE information system CoVax has been updated to capture influenza vaccination records as well as COVID-19 and pneumococcal vaccinations.[137] The current CoVax system captures data relating to the administration of influenza, COVID-19 and pneumococcal vaccines administered in all publicly funded settings. This technology collects information such as risk status and whether the individual is a healthcare worker; these data will inform future analyses. At present, with respect to influenza vaccinations, the CoVax system collects data relating to all influenza vaccinations administered in the community pharmacy setting using a portal called PharmaVax that captures those reimbursed by the HSE and those administered privately. CoVax also collates data relating to influenza vaccinations administered in general practice; these data are collected through the normal GP systems and GPVax portal and include only those vaccinations reimbursed by the HSE.

While there have been improvements in terms of the completeness of these vaccination uptake data, they are currently not linked to outcome data. Furthermore, documentation of a person's risk status may be limited to capturing a single criterion. For example, a 65 year old with diabetes and heart failure would be eligible

for free at the point of delivery vaccination based on both age and having documented medical risks that increase the risk of severe disease. However, they may have only had their age captured as their risk category. As such, a limitation of the analysis in this HTA is that data relating to incidence of influenza and associated clinical outcomes (such as hospitalisation, hospital LOS, mortality) lacked information relating to patients' risk status (that is, the presence of long-term conditions that increase their risk of severe disease) and vaccination status. Therefore, it is not known what proportion of the observed morbidity and mortality occurred in those with multiple long-term conditions or in those who were vaccinated.

Using HIPE data, the cost of care associated with seasonal influenza in acute hospitals was estimated at approximately €6.03 million per annum. However, it is acknowledged that this is likely an underestimate as not all influenza cases are tested and some discharges may not be coded. Moreover, it should be noted that HIPE data are reported by calendar year, whereas HPSC data are reported by influenza season. As such, HIPE data may not accurately capture differences in disease severity and healthcare burden from one influenza season to the next. Again, it is noted that this cost of care in acute hospitals is in the context of an existing immunisation programme. The economic burden associated with influenza 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, disability related to disease complications, or premature death.[127] Although limited research has been published on the total economic burden of influenza in Ireland, international estimates suggest that the burden, including both direct and indirect costs, is likely to be considerable. This will be explored further in Chapter 6.

In conclusion, while there is evidence of year-on-year variability and the data reported likely underestimate the total burden, there is evidence that influenza is associated with a substantial burden in those aged 65 years and older. This burden increases with increasing age and is in the context of an existing HSE Seasonal Influenza Vaccination Programme that offers a standard QIV to this cohort.

4 Review of the effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza

Key points

- Vaccine effectiveness (VE) may be reduced in older adults due to immunosenescence, a natural part of the ageing process. Enhanced inactivated influenza vaccines (IIVs) aim to improve the effectiveness of vaccination relative to standard IIVs.
- To examine the effectiveness of standard IIVs, pooled VE estimates were calculated using published data from the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) groups in Europe. VE was considerably lower in adults aged 65 years and older (34.0%, 95% confidence interval (CI): 23.6 to 43.0) compared with adults aged 18 to 64 years (51.6%, 95% CI: 45.1 to 57.3), with the highest effectiveness observed in children aged less than 18 years (57.7%, 95% CI: 35.7 to 72.1).
- In March 2024, the European Centre for Disease Prevention and Control (ECDC) published an update of their 2020 systematic review of the effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in adults aged 18 years and older. The findings of this update, which were used to inform HIQA's assessment of the safety and effectiveness of specified enhanced IIVs (MF-59® adjuvanted, high-dose, recombinant, cell-based) in adults aged 65 years and older, are summarised in this chapter.
- The updated review included a total of 59 studies, of which 17 studies reported efficacy and or effectiveness data and 42 studies reported safety data. For primary efficacy and or effectiveness outcomes, included studies were limited to those that reported prevention of laboratory-confirmed influenza.
- Considering the effectiveness and safety of MF-59® adjuvanted IIVs (aIIVs) compared with standard IIVs:
    - relative VE (rVE) against laboratory-confirmed influenza (any influenza) ranged from 19% (95% CI: -10 to 41) to 42% (95% CI: -8 to 69), based on three non-randomised study of interventions (NRSIs) when considering evidence specific to adults aged 60 or 65 years and older.

- rVE against laboratory-confirmed influenza-related hospitalisation was 59.2% (95% CI: 14.6 to 80.5) based on one NRSI which was limited to adults aged 65 years and older (moderate certainty of evidence).
- There may be little to no difference in the relative risk (RR) of serious adverse events (SAEs) based on three randomised-controlled trials (RCTs) (RR: 0.95, 95% CI: 0.19 to 4.72), all of which were limited to adults aged 65 years and older (low certainty of evidence).
- Differences in systemic and local adverse reactions were reported. There was a significant increase in the risk of fever (RR 1.95, 95% CI: 1.35 to 2.80) and pain at the injection site (RR 1.94, 95% CI: 1.58 to 2.40) with aIIVs compared with standard IIVs.

- Considering the effectiveness and safety of high-dose IIVs (HD-IIVs) compared with standard IIVs:
  - rVE against laboratory-confirmed influenza was 24.2% (95% CI: 9.7 to 36.5%) based on one RCT limited to adults aged 65 years and older (low certainty of evidence).
  - rVE against laboratory-confirmed influenza-related hospitalisation was 27% (95% CI: -1 to 48) based on one NRSI limited to adults aged 65 years and older (low certainty of evidence).
  - There may be little to no difference in SAEs compared with standard IIVs, with a RR of 1.02 (95% CI: 0.42 to 2.46) based on six RCTs (low certainty of evidence). Five of the RCTs related to adults aged 60 or 65 years and older.
  - However, differences in systemic and local adverse reactions were reported. There was a significant increase in the risk of headache (RR 1.25, 95% CI: 1.13 to 1.40), fever (RR 1.78, 95% CI: 1.25 to 2.54), pain at injection site (RR 1.52, 95% CI: 1.29 to 1.80) and swelling at injection site (RR 1.85, 95% CI: 1.27 to 2.71) with HD-IIVs compared with standard IIVs.
- Considering the effectiveness and safety of cell-based IIVs (ccIIV) compared with standard IIVs in adults aged 18 years and older:
  - rVE against laboratory-confirmed influenza ranged from -5.8% (95% CI: -36.1 to 17.7) (influenza A) to 21.4% (95% CI: -7.3 to 42.4) (influenza B)

based on two NRSIs in adults of mixed age ranges (low certainty of evidence).

  - rVE against laboratory-confirmed influenza-related hospitalisation was 8.5% (95% CI: -75.9 to 52.3) based on one NRSI in adults aged 18 years and older (low certainty of evidence).

  - ccIIVs may or may not decrease SAEs compared with standard IIVs, with a RR of 0.39 (95% CI: 0.02 to 9.49) based on one RCT in adults aged 50 years and older (low certainty of evidence).

  - However, there was a difference in local adverse reactions reported. A significantly increased risk of pain at the injection site (RR 1.19, 95% CI: 1.03 to 1.37) was observed with ccIIVs compared with standard IIVs.

- Considering the effectiveness and safety of recombinant haemagglutinin (HA) IIVs (RIIVs), compared with standard IIVs, in adults aged 18 years and older:

  - rVE against laboratory-confirmed influenza was 30% (95% CI: 10 to 47) based on one RCT in adults aged 50 years and older (moderate certainty of evidence). Subgroup analysis by age indicated an rVE of 17% (95% CI: -20 to 43) in those aged 65 years and older.

  - rVE against laboratory-confirmed influenza-related hospitalisation ranged from -7.3% (95% CI: -52.1 to 24.4) for those aged 18- 49 years to 16.3% (95% CI: -8.7 to 35.5) for those aged 50- 64 years, based on one RCT in adults (certainty of evidence not assessed).

  - RIIVs may or may not result in an increase in SAEs compared with standard IIVs, with a RR of 3.04 (95% CI: 0.32 to 29.10) based on two RCTs in adult populations aged 18 to 64 years (low certainty of evidence).

  - There was no significant difference reported for systemic or local adverse events observed with RIIVs compared with standard IIVs.

- No study reported effectiveness data in relation to influenza-related death.

- Based on the identification and availability of evidence specifically relating to adult populations aged 65 years and older, the findings of the updated review concerning MF-59® aIIVs and HD-IIVs are considered applicable to adults aged 65 years and older. The applicability of the results relating to ccIIVs and RIIVs is less clear, as the majority of studies included populations of mixed age ranges from 18 years and older.

- Overall, while the evidence on the rVE of enhanced IIVs compared with standard IIVs is limited, for the population aged 65 years and older there is some evidence of a statistically significant reduction in influenza-related hospitalisations with aIIVs and for a statistically significant reduction in laboratory-confirmed influenza with HD-IIVs, with each of these findings based on single studies, and limited to data collected over two consecutive influenza seasons.
- While the certainty of evidence was generally low, a larger evidence base is available on safety, with no increased risk of vaccine-related SAEs with any of the four enhanced IIVs considered. Although an increased risk of systemic and or local adverse reactions was reported with three of the enhanced IIVs considered, these vaccines generally appear to be well tolerated.

4.1 Introduction

The HTA Directorate Evaluation Team previously completed a systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals 18 years and older. This systematic review included literature published up to 7 February 2020 (hereafter referred to as the 'primary review'),[10] and was completed under contract with the European Centre for Disease Prevention and Control (ECDC), who published it in August 2020. Researchers at the Robert Koch Institute (Germany) have since updated this systematic review up to 24 July 2023, again under contract with the ECDC, hereafter referred to as the 'updated review'.[138] The findings of this update have been used to inform HIQA's assessment of the safety and effectiveness of the enhanced inactivated influenza vaccines (IIVs) in adults aged 65 years and older, with the results summarised in this chapter.

The population of interest to this HTA is adults aged 65 years and older. To provide some context, Section 4.2 gives a brief overview of the effectiveness of standard IIVs in older adults given their current use by the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme for adults. The subsequent sections summarise the findings of the updated review regarding the effectiveness and safety of enhanced IIVs relative to standard IIVs, including the applicability of these findings to adults aged 65 years and older.

4.2 Vaccine effectiveness

4.2.1 Standard influenza vaccines

Chapter 2 provided a description of the formulation of standard influenza vaccines including both trivalent and quadrivalent inactivated influenza vaccines (IIVs) and

live attenuated influenza vaccines (LAIVs), with the latter authorised for use in those aged 2 to 17 years. An important limitation of standard IIVs is that the immune responses produced can be suboptimal and not long-lasting, particularly in individuals with a compromised immune system and in older adults.[139] Older adults may experience increased susceptibility to influenza infection, and higher influenza-associated morbidity and mortality, as a result of comorbidities and immunocompromising medications or therapies. Immunosenescence is also a significant contributing factor to increased susceptibility to influenza infection in older adults. Immunosenescence is a part of the ageing process, defined as a decline in the body's ability to fight infection, mount sufficient protective immune responses, and generate immunological memory for future protection.[140] This explains why standard IIVs are generally less effective in older adults, compared with younger individuals.

Vaccine effectiveness is a measure of how well vaccination protects people against health outcomes, such as infection, symptomatic illness, hospitalisation or death. Generally it is measured by comparing the frequency of outcomes in vaccinated and unvaccinated people. Vaccine efficacy or effectiveness is typically calculated as:

$$VE = [1\text{-vaccine effect ratio}] \times 100$$

The vaccine effect is as reported in the primary study or studies — for example, an odds ratio, relative risk, hazard ratio or incidence rate ratio.

Absolute vaccine effectiveness (aVE) is a term to describe when a study compares outcomes in a vaccinated with an unvaccinated cohort. Relative VE (rVE) is often used to compare outcomes in cohorts receiving two different vaccine types. In the case of influenza, rVE is commonly used to demonstrate the additional preventive benefit of enhanced IIVs (that is, adjuvanted, high-dose, recombinant and cell-based vaccines) versus standard IIVs.[141]

For the purposes of this HTA, rVE was defined as the additional preventive benefit of enhanced IIVs versus standard IIVs.[141] This may be best explained using an example:

Consider a clinical trial with 1,000 unvaccinated people in the control arm of whom 100 get influenza. By comparison, in a matched vaccinated cohort of 1,000 individuals receiving a standard IIV with a reported aVE of 30%, 70 people would be expected to get influenza. If this vaccinated group instead receive an enhanced IIV with a reported rVE of 24%, you would expect almost a quarter of these 70 cases to be prevented, that is, in total 53 cases of influenza would be expected.

To examine the effectiveness of standard IIVs, pooled vaccine effectiveness (VE) estimates were calculated using published data from the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) groups in Europe.[142-150] These estimates consider the effectiveness of influenza vaccination relative to no vaccination. While they potentially include enhanced vaccines, these data relate to influenza seasons from 2008-2009 to 2019-2020 and as such generally pre-date the widespread availability of the enhanced vaccines (earliest EMA authorisation 2018, see Section 2.4.1). Where reported, enhanced vaccines accounted for a small minority of vaccine use in the included study populations. These data also include use of LAIV; where reported, they similarly accounted for a small proportion of vaccine use and were in the context of paediatric use. As such, the data were considered a broadly accurate reflection of the effectiveness of standard influenza vaccines. Published VE data were identified for individuals aged less than 18 years, 18 to 64 years, 65 years and older, and all ages. It should be noted that the age bands represent a reasonable proxy, as they were not consistent across each study, with some variation between 15 and 18 years and between 60 and 64 years for the age cut-offs. Vaccine effectiveness estimates were converted to relative risks, and then log-transformed with confidence bounds to calculate variance for meta-analysis. Multiple observations were available for some seasons, which could give rise to bias in a pooled analysis. Therefore, estimates within a season were pooled prior to pooling across seasons. As displayed in Table 4.1, VE was considerably lower in adults aged 65 years and older (34.0%, 95% confidence interval (CI): 23.6 to 43.0) compared with adults aged 18 to 64 years (51.6%, 95% CI: 45.1 to 57.3), with the highest effectiveness observed in children aged less than 18 years (57.7%, 95% CI: 35.7 to 72.1). There was a shift from trivalent to quadrivalent influenza vaccines over time, but it has been demonstrated that these types of influenza vaccines overall have similar efficacy profiles.[151] As noted in Chapter 2, for the 2024-2025 and future influenza seasons, it is likely that the formulation of standard influenza vaccines will revert to trivalent vaccines only, given the March 2024 recommendation from the EMA's Emergency Task Force.[28]

Table 4.1. Vaccine effectiveness of standard influenza vaccines in Europe from multiple influenza seasons stratified by age band

Analysis[a]	Vaccine effectiveness (95% CI)
Children (<18 years)	57.7 (35.7 to 72.1)
Adults (18 to 64 years)	51.6 (45.1 to 57.3)
Older adults (≥65 years)	34.0 (23.6 to 43.0)
Overall (all ages)	47.7 (37.1 to 56.5)

Note: CI – confidence interval.
Source data: Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) for the 2008-2009, 2009-2010, 2010-2011, 2012-2013, 2015-2016, 2016-2017, 2022-2023 influenza seasons.[142-150]
[a]Sensitivity analysis with one observation per season.

These estimates highlight the suboptimal effectiveness of standard IIVs in older adults and the requirement for new vaccine technologies to improve effectiveness in this cohort. As outlined in Chapter 2, enhanced IIVs aim to enhance the immunogenicity of the vaccines in older adults, such as through the use of adjuvants or increased antigen doses.[140] The following sections summarise the effectiveness and safety of enhanced IIVs relative to standard IIVs for the prevention of laboratory-confirmed influenza.

4.3 Summary of the methods used in the updated ECDC review

4.3.1 Research questions

The updated review aimed to answer the following research questions:

- What is the efficacy, effectiveness and safety of trivalent and quadrivalent egg-based MF-59® adjuvanted seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent and quadrivalent egg-based high-dose seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent and quadrivalent cell-based seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent and quadrivalent recombinant HA seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?

- What is the efficacy, effectiveness and safety of a quadrivalent messenger RNA (mRNA)-based influenza vaccine by influenza type, subtype (clade if available), age and risk group?

Differences were noted in the research questions and the inclusion criteria between the primary and updated reviews. Specifically, included studies for the effectiveness assessment in the updated review were limited to those that reported prevention of laboratory-confirmed influenza. In addition, for both effectiveness and safety outcomes, the updated review excluded study designs which did not include comparators. The evidence presented in this chapter is limited to that which met the inclusion criteria of the updated review.

See Table 4.2 for the Population, Intervention, Comparator and Outcomes (PICO) framework that was developed in the updated review to address the above research questions.

Table 4.2 Population, intervention, comparator and outcomes framework for the updated review

Population	Subjects aged ≥18 years irrespective of health status or setting.
Intervention	One of the following newer and enhanced seasonal influenza vaccines: ▪ adjuvanted trivalent or quadrivalent vaccine ▪ high-dose trivalent or quadrivalent inactivated vaccine ▪ trivalent or quadrivalent inactivated cell-based vaccine ▪ recombinant trivalent or quadrivalent HA vaccine ▪ quadrivalent mRNA-based vaccine.*
Comparator	▪ Tri- or quadrivalent standard influenza vaccines or one of the above-mentioned newer and/or enhanced seasonal tri- or quadrivalent influenza vaccines (head-to-head comparison between newer and enhanced vaccines).+
Outcomes	**Efficacy or effectiveness – main outcomes** ▪ Laboratory-confirmed influenza (a positive laboratory diagnosis by PCR, virus culture or antigen detection) ▪ Influenza-related hospitalisation (laboratory-confirmed by PCR, virus culture or antigen detection) ▪ Influenza-related death (laboratory-confirmed by PCR, virus culture or antigen detection). **Efficacy or effectiveness – additional outcomes** ▪ Influenza-related ICU admissions (laboratory-confirmed by PCR, virus culture or antigen detection) ▪ Influenza-associated pneumonia/lower respiratory tract disease (laboratory-confirmed by PCR, virus culture or antigen detection)§ ▪ Influenza-associated cardiovascular disease (laboratory-confirmed by PCR, virus culture or antigen detection)§ ▪ Influenza-like illness (ILI) (symptoms of influenza only). Internationally accepted case definitions to be used (e.g. WHO, US CDC, EU). **Safety – main outcomes** ▪ Serious adverse events (requiring intervention to prevent disability or permanent damage, resulting in disability or permanent damage, initial or prolonged hospital care, congenital anomaly/birth defect, life-threatening, or resulting in death).¥ **Safety – additional outcomes** ▪ Systemic adverse events (e.g. malaise, nausea, fever, arthralgia, myalgia, rash, headache and more generalised and serious signs, such as neurological harms). After consultation with the influenza working group, it was decided to focus the analysis on headache and fever as the most relevant and mainly reported events.§ ▪ Local adverse events (e.g. pain, erythema, oedema/swelling, induration). After consultation with the influenza working group, it was decided to focus the analysis on pain and swelling as the most relevant and mainly reported local adverse events.§

	▪ Adverse pregnancy outcomes after vaccination during pregnancy: spontaneous abortion, fetal death, stillbirth, preterm birth (less than 37 weeks), pre-eclampsia and eclampsia. ▪ Adverse neonatal outcomes after vaccination during pregnancy: congenital malformations (minor and major), neonatal death, and small-for-gestational-age.
Study design	▪ Randomised controlled trials with randomisation either at the individual or cluster level. ▪ Non-randomised studies were considered as long as they had a control group.^

Key: ICU – intensive care unit; PCR – polymerase chain reaction; US CDC – US Centers for Disease Control and Prevention; WHO – World Health Organization.
*Included in the updated review, but not investigated in the primary review.
+Changed from that of the primary review, which included placebo, no vaccination or other type of vaccines as comparators.
§Listed as main outcomes in the primary review, but as additional outcomes in updated review.
¥Updated and different compared with the primary review.
^Study designs which did not include comparators were excluded for efficacy and safety outcomes. In the primary review, such studies were included for safety outcomes.

4.4 Quality appraisal of the updated review on enhanced inactivated influenza vaccines

As noted in Section 4.1, an updated systematic review published by the ECDC in April 2024 was identified as the basis for the assessment of the relative effectiveness and safety of the enhanced IIVs. Two reviewers independently appraised the quality of the updated review using the AMSTAR 2 tool (A Measurement Tool to Assess Systematic Reviews, version 2). The AMSTAR 2 tool is not designed to provide an overall quality score; however, the authors of the tool have proposed that the confidence in the quality of seven critical domains, which can substantially affect the validity of a review and its conclusions, can inform overall confidence in the results of the review.[152] No weaknesses were identified for the seven critical domains or the nine non-critical items. Overall, the updated review was therefore considered to be high quality.

We also assessed the quality of the primary review published by the ECDC in 2020 using the AMSTAR 2 tool. Overall, the primary review was considered high quality, with one non-critical weakness arising from not listing the sources of funding for the included studies. This was considered non-critical as the potential influence of industry funding was explicitly considered in the risk of bias assessment and discussion of the results. The full quality appraisal results for both the primary and the updated review are provided in the supplementary file (Appendix 4.1).

4.5 Summary of the results reported by the updated review

In the primary review,[10] a total of 110 studies were included. Of those, 42 studies (comprising 10 studies on efficacy and or effectiveness and 32 studies on safety) met the inclusion criteria of the updated review and were further considered. In addition, the updated search identified 17 studies (consisting of seven efficacy and or effectiveness studies and 10 safety studies). Thereby, the evidence body of the updated review comprised 59 studies (17 efficacy and or effectiveness studies and 42 safety studies). With the exception of two safety studies where the comparator was another enhanced vaccine, the comparator in all included studies was a standard IIV. No study provided data relating to mRNA influenza vaccines. Subgroup analyses (for example, based on population characteristics such as age group, pregnancy status and comorbidities) were not performed due to lack of data. In Sections 4.5.1 to 4.5.8, the summary of the review findings focuses primarily on outcomes for which results were reported.

The age ranges varied across the included studies, from those that included children and young adults, to those restricted to adults aged 60 or 65 years and older. The population group of interest to this HTA is adults aged 65 years and older. In the updated review, there were 25 studies (comprising eight effectiveness studies and 17 safety studies) that limited inclusion to adults aged 65 years and older. Of these eight effectiveness studies, five related to MF59® adjuvanted IIVs (aIIVs) and included one test-negative study and four case control studies. Three studies related to high-dose IIVs (HD-IIVs) and included two test-negative study designs and one RCT. For cell-based IIVs (ccIIVs) and recombinant HA IIVs (RIIVs), there were no effectiveness studies identified that were specifically conducted in adults aged 65 years and older.

Of the 17 safety studies that limited inclusion to adults aged 65 years and older, eight related to MF59® aIIVs, seven to HD-IIVs, two investigated the safety of RIIVs while no safety studies specific to this age cohort were identified for ccIIVs. A further six studies (comprising one effectiveness study and five safety studies) that limited inclusion to adults aged 60 years and older were included. The single effectiveness case control study related to MF-59® aIIVs. Of the five safety studies, two were RCTs related to HD-IIVs and three were RCTs related to MF-59® aIIVs.

Sub-group analyses by age were not performed in the updated review due to lack of data. In reporting the findings of the updated review, while subgroup analyses were not undertaken, where possible, the number of studies conducted in those aged 65 years and older were highlighted, including the proportion of participants and the weighting these participants contributed to the random-effects meta-analyses.

4.5.1 Efficacy and or effectiveness – MF59® adjuvanted influenza vaccines

The summary of findings from the review relating to the effectiveness of MF59® aIIVs is presented in Table 4.3 below.

Laboratory-confirmed influenza

Seven studies (all NRSI) reported comparative effectiveness data for aIIVs against laboratory-confirmed influenza (any influenza, influenza A [H1N1], A [H3N2] and influenza B).[153-159] The 13 VE estimates reported from these seven studies were highly variable and ranged from -30 to 88%, with only two of the estimates being statistically significant (both favouring the aIIV for specific strains). Due to heterogeneity, meta-analysis was not performed.

Five studies reported vaccine estimates against any influenza, ranging from -1% to 42%, none of which were statistically significant.[153, 155-157, 159] Two of these five studies were conducted in adults aged 65 years and older, with VE of 30% (95% CI: -83 to 73) and 42% (95% CI: -8 to 69), respectively, with each of these estimates relating to a single influenza season.[156, 159] An additional one of these five studies was conducted in those aged 60 years and older, with VE of 19% (95% CI: -10 to 41%) for a single influenza season.[155]

Influenza-related hospitalisation

One NRSI (n=512) was included that examined influenza-related hospitalisations for aIIVs.[160] This study, which included a single country (Italy) subset of the study population included in the Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project, was limited to adults aged 65 years and older, and reported data from two consecutive seasons (2018-2019 and 2019-2020). A statistically significant reduction in hospitalisations was noted with the aIIV. Relative VE against all strains was 59.2% (95% CI: 14.6 to 80.5%) and 63.7% (95% CI: 22.8 to 82.9%) for influenza A.

Influenza-related death

No studies included in the updated review reported on this outcome.

4.5.2 Safety – MF59® adjuvanted influenza vaccines

The summary of findings from the review relating to the safety of MF59® aIIVs is presented in Table 4.3 below.

Serious adverse events

Three RCTs[161-163] and two NRSIs[164, 165] were included that reported serious adverse events (SAEs) associated with MF59® aIIVs. There was no significant difference in the risk of SAEs after vaccination with MF59® aIIVs compared with standard IIVs; the pooled relative risk (RR) was 0.95 (95% CI: 0.19 to 4.72; fixed-effects model) based on the three RCTs, all of which were conducted in adults aged 65 years and older. Across the three RCTs, there were three SAEs reported in the MF-59® aIIV group, including two cases of Guillain-Barré syndrome, and three SAEs reported in the standard IIV group.

Systemic reactions

Ten RCTs were included that reported on headache after vaccination with aIIVs.[161, 162, 166-173] In the random effects model, there was no significant difference in the risk of headache after vaccination with MF59® compared with standard IIVs; the pooled RR was 1.18 (95% CI: 0.94 to 1.48). Of these ten RCTs, five studies were conducted in adults aged 65 years and older and accounted for 81.6% of participants (n=8,232/10,087) and 51.7% of the weighting in the random-effects meta-analysis.[161, 169, 170, 172, 173]

Nine RCTs were included that reported on fever after vaccination with aIIVs.[9, 161, 162, 167-170, 173, 174] The risk of fever following vaccination with aIIVs was significantly higher than with standard IIVs. The pooled RR was 1.95 (95% CI: 1.35 to 2.80; random effects model). Of these nine RCTs, five studies were conducted in adults aged 65 years and older and accounted for 87.1% of participants (n=8,324/10,236) and 59.8% of the weighting in the random-effects meta-analysis.[9, 161, 169, 170, 173]

Local reactions

Twelve RCTs reported on pain at the injection site after vaccination with aIIVs.[9, 161, 162, 166-173, 175] The risk of pain at the injection site following vaccination with aIIVs was significantly higher than with standard IIVs. The pooled RR was 1.94 (95% CI: 1.58 to 2.40; random effects model). Of these 12 RCTs, seven were conducted in adults aged 65 years and older with these accounting for 83.6% of the participants (n=9,443/11,298) and 53.4% of the weighting in the random-effects meta-analysis.[9, 161, 169, 170, 172, 173, 175]

Swelling at the injection site after vaccination with the aIIV was reported in five RCTs.[9, 161, 169, 172, 173] All five RCTs were conducted in adults aged 65 years and older. There was no significant difference in the risk of swelling at the injection site following vaccination with aIIVs compared with standard IIVs. The pooled RR was 1.26 (95% CI: 0.91 to 1.74; random effects model).

Table 4.3 Summary of findings relative effectiveness and safety of MF59®-adjuvanted influenza vaccines versus standard influenza vaccines in adults

Patient or population: Adults (aged ≥18 years)

Setting: All settings

Intervention: MF59®-adjuvanted influenza vaccines

Comparison: Standard influenza vaccines

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	What does this mean?
	Risk with standard influenza vaccines	Risk MF59®-adjuvanted influenza vaccines	Difference				
Laboratory-confirmed influenza	NA	NA	NA	rVE-range -30 (-146 to 31) to 88 (51 to 100)	10,492 (7 observational studies)	⊕⊕◯◯ LOW [a,b]	MF59®-adjuvanted influenza vaccines may or may not reduce laboratory-confirmed influenza infection in adults compared to standard influenza vaccines.
Influenza-related hospitalisation (laboratory confirmed)	NA	NA	NA	rVE 59.2 (14.6 to 80.5)	512 (1 observational study)	⊕⊕⊕◯ MODERATE [a]	MF59®-adjuvanted influenza vaccines probably reduce hospitalisation related to laboratory-confirmed influenza infection in adults compared to standard influenza vaccines.
Influenza-related death (laboratory confirmed)	-	-	-	-	-	-	No data provided.
Serious adverse events	0.1%	0.1% (0 to 0.3)	0.0% fewer (0.1 fewer to 0.3 fewer)	RR 0.95 (0.19 to 4.72)	8,504 (3 RCTs)	⊕⊕◯◯ LOW [c,d]	MF59®-adjuvanted influenza vaccines may result in little to no difference in serious adverse events compared to standard influenza vaccines.

Idiopathic thrombocytopenic purpura	-	-	-	-	-	-	No data provided.
Narcolepsy/ cataplexy	-	-	-	-	-	-	No data provided.
Guillain-Barré syndrome	-	-	-	-	-	-	No data provided.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **rVE:** relative vaccine effectiveness [(1- risk ratio)*100].

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Residual confounding cannot be excluded
b. Heterogeneous point estimates between studies
c. High risk of bias in 2 out of 3 studies
d. Wide confidence interval

Source: European Centre for Disease Prevention and Control, 2024[138]
Table modified to include a column reporting the number of studies (participants).

4.5.3 Efficacy and or effectiveness – high-dose influenza vaccines

The summary of findings from the review relating to the effectiveness of HD-IIVs is presented in Table 4.4 below.

Laboratory-confirmed influenza

Two studies were identified that examined HD-IIVs and laboratory-confirmed influenza.[176, 177] One RCT was included that reported an rVE for HD-IIVs of 24.2% (95% CI: 9.7 to 36.5%) against laboratory-confirmed influenza (all strains) during two consecutive seasons (2011-2012 and 2012-2013).[177] This RCT was limited to adults aged 65 years and older. One NRSI was included that reported rVE estimates for HD-IIVs against influenza A during four consecutive seasons (2015-2016, 2016-2017, 2017-2018 and 2018-2019).[176] Relative VE ranged between -9% and 19%, with none of the estimates being statistically significant. This study was limited to adults aged 65 years and older.

Influenza-related hospitalisation

For the effect of HD-IIVs on influenza-related hospitalisations, one NRSI was identified;[178] this study was conducted in adults aged 65 years and older. Relative VE against hospitalisation due to influenza (laboratory-confirmed) was reported for two consecutive seasons (2015-2016 and 2016-2017) against influenza A, B and all strains separately. Relative VE against all strains was 27% (95% CI: -1 to 48). None of the rVE estimates ranging between 22% and 44% were statistically significant.

Influenza-related death

No studies included in the updated review reported on this outcome.

4.5.4 Safety – High-dose influenza vaccines

The summary of findings from the review relating to the safety of HD-IIVs is presented in Table 4.4 below.

Serious adverse events

Six RCTs[179-184] and two NRSIs[185, 186] were identified that reported on SAEs after administration of a HD-IIV. Four RCTs reported a total of 11 SAEs (including neuropathy, cranial nerve VI palsy, shock, Crohn's disease, myasthenia gravis, encephalomyelitis, rheumatoid arthritis and thyroid neoplasm). There was no significant difference in the risk of SAEs following administration of HD-IIVs compared with standard IIVs; the pooled RR was 1.02 (95% CI: 0.42 to 2.46; fixed-effects model) based on these six RCTs. Of these RCTs, three were conducted in

adults aged 65 years and older,[179, 180, 182] two in adults aged 60 years and older,[183, 184] and one in adults aged 50 to 64 years.[181] Of note, one of the two RCTs in adults aged 60 years and older reported results separately for the 60 to 64 year age group and 65 years and older age group.[183]

The two NRSIs were conducted in adults aged 65 years and older. One NRSI reported no increased risk of Guillain-Barré syndrome in the primary analysis.[185] The second NRSI did not find any increased risk of seizure (RR: 1.03, 95% CI: 0.81 to 1.32), encephalopathy (RR: 0.94, 95% CI: 0.78 to 1.14) or short-term death (RR: 1.09, 95% CI: 0.8 to 1.48) after HD-IIV administration, as compared with a standard IIV.[186]

Systemic adverse events

In relation to headaches, based on pooled data from 10 RCTs, there was a significantly increased risk of headache following vaccination with HD-IIVs compared with standard IIVs; the pooled RR was 1.25 (95% CI: 1.13 to 1.40; random effects model).[9, 180-183, 187-189] Of these 10 RCTs, five were conducted in adults aged 65 years and older[180, 182, 189-191] and another RCT (conducted in adults aged 60 years and older) provided specific results for the subgroup 65 years and older.[183] Estimates from these six RCTs accounted for 80.3% of participants (n=5,927/7,382) and 68.8% of the weighting for the random-effects meta-analysis. A funnel plot and visual inspection for small study effects was performed. No evidence of publication bias was identified.

Fever was reported in nine RCTs and one NRSI that were included in the updated review.[180-182, 186-192] There was a significantly increased risk of fever following vaccination with HD-IIVs compared with standard IIVs. The pooled RR from the nine RCTs was 1.78 (95% CI: 1.25 to 2.54; random effects model).[180-182, 187-192] Of these nine RCTs, five were conducted in adults aged 65 years and older.[180, 182, 189-191] Estimates from these five RCTs accounted for 88.4% of participants (n=5,146/5,824) and 94.2% of the weighting in the random-effects meta-analysis. Separately, the NRSI, conducted in adults aged 65 years and older with end-stage renal disease (ESRD), reported no difference in the risk of fever following vaccination with HD-IIVs compared with standard IIVs (RR 0.92, 95% CI: 0.78 to 1.08).[186]

Local adverse events

Pain at the injection site after vaccination with HD-IIVs was reported in 11 RCTs and one NRSI included in the updated review.[180-184, 186-192] There was a significantly increased risk of pain at the injection site following vaccination with HD-IIVs compared with standard IIVs. The pooled RR was 1.52 (95% CI: 1.29 to 1.80;

random effects model). Of these 11 RCTs, five were conducted in adults aged 65 years and older[180, 182, 189-191] and another RCT (conducted in adults aged 60 years and older) provided specific results for the subgroup 65 years and older.[183] These six RCTs accounted for 62.6% of participants (n=5,927/9,462) and 51.1% of the weighting in the random-effects meta-analysis.

The NRSI,[186] conducted in adults aged 65 years and older with ESRD, also reported a significantly increased risk of pain at the injection site following vaccination with HD-IIVs compared with standard IIVs; (RR 1.23, 95% CI: 1.12 to 1.34). A funnel plot and visual inspection for small study effects was performed. No evidence of publication bias was identified.

Injection site swelling after vaccination was reported in eight RCTs included in the updated review.[180-182, 187-190, 192] There was a significantly increased risk of swelling at the injection site following vaccination with HD-IIVs compared with standard IIVs. The pooled RR was 1.85 (95% CI: 1.27 to 2.71; random-effects model). Of these eight RCTs, four were conducted in adults aged 65 years and older.[180, 182, 189, 190] These four RCTs accounted for 88.2% of participants (n=5,050/5,728) and 78.1% of the weighting in the random-effects meta-analysis.

Table 4.4 Summary of findings relative effectiveness and safety of high-dose influenza vaccines versus standard influenza vaccines in adults

Patient or population: Adults (aged ≥18 years)

Setting: All settings

Intervention: High-dose influenza vaccines

Comparison: Standard influenza vaccines

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	What does this mean?
	Risk standard influenza vaccines	Risk high-dose influenza vaccines	Difference				
Laboratory-confirmed influenza	1.9%	1.4% (1.2 to 1.7)	0.5% fewer (0.7 fewer to 0.2 fewer)	rVE 24.2 (9.7 to 36.5)~	31,989 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	High-dose influenza vaccines probably slightly reduce laboratory-confirmed influenza infection in adults.
Influenza-related hospitalisation (laboratory confirmed)	NA	NA	NA	rVE 27 (-1 to 48)	1,107 (1 NRSI)	⊕⊕◯◯ LOW [b,c]	High-dose influenza vaccines may slightly reduce hospitalisations related to laboratory-confirmed influenza infection in adults.
Influenza-related death (laboratory confirmed)	-	-	-	-	-	-	No data provided.
Serious adverse events	0.2%	0.2% (0.1 to 0.6)	0.0% fewer (0.1 fewer to 0.4 fewer)	RR 1.02 (0.42 to 2.46)	9,034 (6 RCTs)	⊕⊕◯◯ LOW [c,d]	High-dose influenza vaccines may result in little to no difference in serious adverse events (SAEs) related to vaccination.
Idiopathic thrombocytopenic purpura	-	-	-	-	-	-	No data provided.

Narcolepsy/ cataplexy	-	-	-	-	-	-	No data provided.
Guillain-Barré syndrome	-	-	-	-	-	-	No data provided.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **NRSI**: Non-randomised study of intervention; **RCT**: Randomised-controlled trial; **RR:** Risk ratio; **rVE:** relative vaccine effectiveness [(1- risk ratio)*100].

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations
a. One RCT with moderate risk of bias
b. Residual confounding cannot be excluded
c. Wide confidence interval
d. 3 out of 5 studies moderate risk of bias

Source: European Centre for Disease Prevention and Control, 2024[138]
Note: Table modified to include a column reporting the number of studies (participants) and amending one figure.

~Figure taken from original study.[177]

4.5.5 Efficacy and or effectiveness – Cell-based influenza vaccines

The summary of findings from the review relating to the effectiveness of ccIIVs is presented in Table 4.5 below.

Laboratory-confirmed influenza

Two NRSIs were identified that reported rVE of ccIIVs against laboratory-confirmed influenza. One study reported on laboratory-confirmed influenza (all strains and A/H3N2) during two seasons (2014-2015 and 2017-2018) for a range of adult populations, but reported results for the sub-group of adults aged 65 years and older.[193] The second NRSI, which included participants aged from 4 to 64 years, reported rVE estimates against influenza A and B during one season (2017-2018).[194] Relative VE in these two studies ranged between -5.8% and 21.4%, with none of the estimates being statistically significant.

Influenza-related hospitalisation

For the effect of ccIIVs on the outcome influenza-related hospitalisations, one NRSI was identified that was conducted in adults aged 18 years and older.[195] Relative VE against hospitalisation due to influenza (laboratory-confirmed) was reported for one season (2017-2018), against influenza A and B separately. None of the rVE estimates, which ranged between 1.8 and 24.9%, were statistically significant.

Influenza-related death

No studies included in the updated review reported on this outcome.

4.5.6 Safety – Cell-based influenza vaccines

The summary of findings from the review relating to the safety of ccIIVs is presented in Table 4.5 below.

Serious adverse events

One RCT, conducted in adults aged 50 years and older, reported one SAE (hypersensitivity) after ccIIV administration.[196] No difference was noted in the risk of SAEs relative to standard IIVs (RR: 0.39 (95% CI: 0.02 to 9.49; fixed-effects model)).

Systemic adverse events

Headache after ccIIV vaccine administration was reported from six RCTs.[196-201] These studies include adult populations aged 18 years and older. There was no significant difference in the risk of headache following vaccination with ccIIVs

compared with standard IIVs. The pooled RR was 1.02 (95% CI: 0.94 to 1.11; random-effects model).

Six RCTs, all including adult populations aged 18 years and older, were included in the updated review which provided data on fever after vaccination with ccIIVs.[196-201] Using a random effects model, there was no significant difference in the risk of fever following vaccination with ccIIVs compared with standard IIVs (pooled RR 1.00, 95% CI: 0.69 to 1.45).

Local adverse events

For pain at the injection site after vaccination with ccIIVs, the updated review reported data from five RCTs.[196-198, 200, 201] There was a significantly increased risk of pain at the injection site following vaccination with ccIIVs compared with standard IIVs (RR 1.19, 95% CI: 1.03 to 1.37; random effects model). These RCTs included adult populations aged 18 years and older.

The risk of swelling at the injection site after vaccination with ccIIVs was reported in six RCTs included in the updated review.[196-201] No difference in the risk of swelling at the injection site compared with standard IIVs (RR 1.10, 95% CI: 0.88 to 1.37; random effects model). These RCTs included adult populations aged 18 years and older.

Table 4.5 Summary of findings relative effectiveness and safety of cell-based influenza vaccines versus standard influenza vaccines in adults

Patient or population: Adults (aged ≥18 years)

Setting: All settings

Intervention: Cell-based influenza vaccines

Comparison: Standard influenza vaccines

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	What does this mean?
	Risk standard influenza vaccines	Risk cell-based influenza vaccines	Difference				
Laboratory-confirmed influenza	NA	NA	NA	rVE-range -5.8 (-36.1 to 17.7) to 21.4 (-7.3 to 42.4)	1,025,097 (2 observational studies)	⊕⊕◯◯ LOW [a]	Cell-based influenza vaccines may or may not reduce laboratory-confirmed influenza infection in adults.
Influenza-related hospitalisation (laboratory confirmed)	NA	NA	NA	rVE 8.5 (-75.9 to 52.3)	1,741 (1 observational study)	⊕⊕◯◯ LOW [a,b]	Evidence is uncertain whether cell-based influenza vaccines reduce hospitalisation related to laboratory-confirmed influenza in adults.
Influenza-related death (laboratory confirmed)	-	-	-	-	-	-	No data provided.
Serious adverse events	NA	NA	NA	RR 0.39 (0.02 to 9.49)	3,208 (1 RCT)	⊕⊕◯◯ LOW [b]	Cell-based influenza vaccines may or may not decrease serious adverse events (SAEs) related to vaccination.
Idiopathic thrombocytopenic purpura	-	-	-	-	-	-	No data provided.

Narcolepsy/ cataplexy	-	-	-	-	-	-	No data provided.
Guillain-Barré syndrome	-	-	-	-	-	-	No data provided.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RCT**: Randomised-controlled trial; **RR:** Risk ratio; **rVE:** relative vaccine effectiveness [(1- risk ratio)*100].

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Residual confounding cannot be excluded
b. Wide confidence interval

Source: European Centre for Disease Prevention and Control, 2024[138]

Table modified to include a column reporting the number of studies (participants).

4.5.7 Efficacy and or effectiveness – Recombinant HA influenza vaccines

The summary of findings from the review relating to the effectiveness of RIIVs is presented in Table 4.6 below.

Laboratory-confirmed influenza

Two studies, one RCT and one NRSI, were included that examined the effect of RIIVs on laboratory-confirmed influenza. The one RCT,[202] conducted in adults aged 50 years and older, reported rVE estimates for RIIVs from one season (2014-2015) for all strains and influenza A and B separately. Relative VE against all strains was 30% (95% CI: 10 to 47%), while it was 36% (95% CI: 14 to 53%) against influenza A and 4% (95%CI: -42 to 56%) against influenza B. Additional subgroup analysis by age presents a significant effect for those aged 50 to 64 years (rVE: 42% (95% CI: 15 to 61), but not for those aged 65 years and older (rVE: 17% (95% CI: -20 to 43). The one NRSI,[203] conducted in adults aged 18 years and older, reported rVE estimates for RIIVs (all strains) during two consecutive seasons (2018-2019 and 2019-2020). Relative VE ranged between -3% (95% CI: -52 to 30) and 6% (95% CI: -48 to 40), with none of the estimates being statistically significant.

Influenza-related hospitalisation

For the effect of RIIVs on the outcome influenza-related hospitalisation, one cluster-RCT,[204] conducted in adults aged 18 to 64 years, was included that reported rVE data for RIIVs across two separate age groups obtained during two consecutive seasons (2018-2019 and 2019-2020). Relative VE was -7.3% (95% CI: -52.1 to 24.4%) for the age group 18 to 49 years and 16.3% (95% CI: -8.7 to 35.5%) for the age group 50 to 64 years.

Influenza-related death

No studies included in the updated review reported on this outcome.

4.5.8 Safety – Recombinant HA influenza vaccines

The summary of findings from the review relating to the safety of RIIVs is presented in Table 4.6 below.

Serious adverse events

Two RCTs and two NRSIs were included that reported SAEs after administration of RIIVs. The two RCTs,[205, 206] one conducted in adults aged 18 to 55 years and one in adults aged 50 to 64 years, reported two SAEs (syncope; pericardial effusion) after

administration of RIIVs. For the two RCTs, the pooled RR of SAEs after vaccination with RIIVs compared with standard IIVs showed no difference in the risk of SAEs (RR 3.04, 95% CI: 0.32 to 29.10; fixed-effects model).

The two NRSIs were conducted in adults aged 18 years and older.[204, 207] One NRSI reported no significantly increased risk of death (odds ratio (OR) 0.49, 95% CI: 0.21 to 1.05), idiopathic thrombocytopenic purpura (OR 0.90, 95% CI: 0.03 to 11.81), non-infectious pleural effusion (OR 1.76, 95% CI: 0.05 to 68.70) and convulsion (OR 0.90, 95% CI: 0.03 to 11.81) following administration of RIIVs, compared with standard IIVs.[204] The other NRSI found no increased risk of Guillain-Barré syndrome in inpatient or emergency department settings (OR 0.00, 95% CI: 0.00 to 16.07) or in outpatients (OR 0.00, 95% CI: 0.00 to 112.6).[207] Furthermore, they did not detect an increased risk of non-infectious pleural effusion (OR 0.00, 95% CI: 0.00 to 4.8) or narcolepsy and or cataplexy (OR 0.00, 95% CI: 0.00 to 6).

Systemic adverse events

Headache after administration of RIIVs was reported by five RCTs included in the updated review,[202, 205, 208-210] of which two RCTs were conducted in adults aged 65 years and older.[209, 210] There was no significant difference in the risk of headache following administration of RIIVs compared with standard IIVs (RR 0.80, 95%CI: 0.52 to 1.24; random effects model). The two studies in adults aged 65 years and older accounted for 9.2% of the participants (n=1,068/11,668) and 35.3% of the weighting in the random-effects meta-analysis.[209, 210]

Two NRSIs,[204, 207] conducted in adults aged 18 years and older, were included that reported data on fever after administration of RIIVs, neither of which found an increased risk of fever.

Local adverse events

Seven RCTs were included that reported data on pain at the injection site after administration of RIIVs.[9, 202, 205, 208-211] There was no significant difference in the risk of pain at the injection site following administration of RIIVs compared with standard IIVs (pooled RR 0.92, 95% CI: 0.84 to 1.00; random effects model). Three of the seven RCTs were conducted in adults aged 65 years and older and accounted for 12.7% of the participants (n=1,911/15,094) and 15.1% of the weighting in the random-effects meta-analysis.[9, 209, 210]

Data on injection site swelling after administration of RIIVs were provided by six RCTs included in the updated review.[9, 202, 205, 208-210] There was no significant difference in the risk of swelling at the injection site following administration of RIIVs compared with standard IIVs (pooled RR 0.94, 95% CI: 0.64 to 1.39; random effects

model). Three of the six RCTs were conducted in adults aged 65 years and older and accounted for 15.5% of the participants (n=1,911/12,367) and 39.5% of the weighting in the random-effects meta-analysis.[9, 209, 210]

Table 4.6 Summary of findings relative effectiveness and safety of recombinant influenza vaccines versus standard influenza vaccines in adults

Patient or population: Adults (aged ≥18 years)

Setting: All settings

Intervention: Recombinant influenza vaccines

Comparison: Standard influenza vaccines

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	What does this mean?
	Risk standard influenza vaccines	Risk recombinant influenza vaccines	Difference				
Laboratory-confirmed influenza	3.1%	2.2% (1.7 to 2.8)	0.9% fewer (1.5 fewer to 0.3 fewer)	rVE 30 (10 to 47)	8,855 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	Recombinant influenza vaccines probably slightly reduce laboratory-confirmed influenza infection in adults.
Influenza-related hospitalisation (laboratory confirmed)	Certainty of the evidence could not be assessed due to a lack of information			-	-	-	NA
Influenza-related death (laboratory confirmed)	-	-	-	-	-	-	No data provided.
Serious adverse events	NA	NA	NA	RR 3.04 (0.32 to 29.10)	907 (2 RCTs)	⊕⊕◯◯ LOW [b]	Recombinant influenza vaccines may or may not result in an increase in serious adverse events (SAEs) related to vaccination.

Idiopathic thrombocytopenic purpura	NA	NA	NA	OR 0.52 (0.15 to 1.50)	42,684 (1 observational study)	⊕⊕◯◯ LOW [c,d]	Recombinant influenza vaccines may or may not result in a decrease in idiopathic thrombocytopenic purpura related to vaccination.
Narcolepsy/cataplexy	NA	NA	NA	OR 0 (0 to 6)	305,659 (1 observational study)	⊕◯◯◯ VERY LOW [d,e]	Evidence is uncertain about the effect of recombinant influenza vaccines on narcolepsy/cataplexy related to vaccination.
Guillain-Barré syndrome	NA	NA	NA	OR 0.00 (0.00 to 16.07)	305,659 (1 observational study)	⊕◯◯◯ VERY LOW [d,e]	Evidence is uncertain about the effect of recombinant influenza vaccine on Guillain-Barré syndrome related to vaccination.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT**: Randomised-controlled trial; **RR:** Risk ratio; **rVE:** relative vaccine effectiveness [(1- risk ratio)*100].

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations
a. One RCT with moderate risk of bias
b. Two RCTs with moderate risk of bias
c. Residual confounding cannot be excluded
d. Wide confidence interval
e. No adjustment for comorbidities, even though there was a significant difference between the groups

Source: European Centre for Disease Prevention and Control, 2024[138]
Table modified to include a column reporting the number of studies (participants).

4.6 Discussion

This chapter considered the available evidence in relation to the efficacy, effectiveness and safety of enhanced IIVs in adults aged 65 years and older. These enhanced IIVs aim to improve immunogenicity relative to standard IIVs, thereby increasing their effectiveness in this cohort. Such strategies are required because standard IIVs have been demonstrated to elicit a suboptimal immune response in older adults, compared with younger populations. This suboptimal response relative to younger populations is evident from the vaccine effectiveness estimates derived from pooling estimates based on published data from the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) groups in Europe. A high quality systematic review update from the ECDC published in March 2024 reported on the effectiveness and safety of four types of enhanced IIVs in adults aged 18 years and older; MF59® aIIVs, HD-IIVs, ccIIVs, and RIIVs. Findings from this update were used to inform HIQA's assessment of the relative effectiveness and safety of these vaccines in adults aged 65 years and older.

4.6.1 Relative efficacy, effectiveness and safety of enhanced inactivated influenza vaccines

For the MF59® aIIVs, rVE against laboratory-confirmed influenza (considering both any influenza and specifically influenza A [H1N1], A [H3N2] and influenza B) ranged from -30% (95% CI: -146 to 31) to 88% (95% CI: 51 to 100) based on seven NRSIs of mixed age ranges (low certainty of evidence). When restricted to the population aged 60 or 65 years and older, rVE (any influenza) ranged from 19% (95% CI: -10 to 41%) to 42% (95% CI: -8 to 69) with each of these estimates relating to a single flu season. Relative VE against laboratory-confirmed influenza-related hospitalisation was 59.2% (95% CI: 14.6 to 80.5) based on one NRSI in adults aged 65 years and older (moderate certainty of evidence). MF59® aIIVs may result in little to no difference in SAEs compared with standard IIVs, with a RR of 0.95 (95% CI: 0.19 to 4.72), based on three RCTs in adults aged 65 years and older (low certainty of evidence). However, differences in systemic and local adverse reactions were reported. There was a significant increase in the risk of fever (RR 1.95, 95% CI: 1.35 to 2.80) and pain at the injection site (RR 1.94, 95% CI: 1.58 to 2.40) with aIIVs compared with standard IIVs.

For the HD-IIVs, rVE against laboratory-confirmed influenza was 24.2% (95% CI: 9.1 to 36.5) in one RCT in adults aged 65 years and older (low certainty of evidence). Relative VE against laboratory-confirmed influenza-related hospitalisation was 27% (95% CI: -1 to 48) based on one NRSI in adults aged 65 years and older (low certainty of evidence). High-dose IIVs may result in little to no difference in SAEs compared with standard IIVs, with a RR of 1.02 (95% CI: 0.42 to 2.46) based

on six RCTs (low certainty of evidence). Three of these RCTs were in adults aged 65 years and older, two in adults aged 60 years and older (of which one provided specific data for adults aged 65 years and older), and one in adults aged 50 to 64 years. However, differences in systemic and local adverse reactions were reported. There was a significant increase in the risk of headache (RR 1.25, 95% CI: 1.13 to 1.40), fever (RR 1.78, 95% CI: 1.25 to 2.54), pain at injection site (RR 1.52, 95% CI: 1.29 to 1.80) and swelling at injection site (RR 1.85, 95% CI: 1.27 to 2.71) with HD-IIVs compared with standard IIVs.

For the ccIIVs, rVE against laboratory confirmed influenza ranged from -5.8% (95% CI: -36.1 to 17.7) (influenza A) to 21.4% (95% CI: -7.3 to 42.4) (influenza B) based on two NRSIs in adult populations of mixed age ranges (low certainty of evidence). Relative VE against laboratory-confirmed influenza-related hospitalisation was 8.5% (95% CI: -75.9 to 52.3) based on one NRSI in adults aged 18 years and older (low certainty of evidence). Cell-based IIVs may or may not decrease SAEs compared with standard IIVs, with a RR of 0.39 (95% CI: 0.02 to 9.49) based on one RCT in adults aged 50 years and older (low certainty of evidence). However, there was a difference in local adverse reactions reported. A significantly increased risk of pain at the injection site (RR 1.19, 95% CI: 1.03 to 1.37) was observed with ccIIVs compared with standard IIVs.

For the RIIVs, rVE against laboratory confirmed influenza was 30% (95% CI: 10 to 47) in one RCT in adults aged 50 years and older (moderate certainty of evidence); however, additional subgroup analysis by age indicated that this was not statistically significant for those aged 65 years and older (rVE: 17% (95% CI: -20 to 43). Further evidence based on one NRSI of high-risk adults aged 18 years and older suggested an rVE that ranged from -3% (95% CI: -52 to 30) to 6% (95% CI: -48 to 40) (certainty of evidence not assessed). Relative VE against laboratory-confirmed influenza-related hospitalisation ranged from -7.3% (95% CI: -52.1 to 24.4), for the age group 18 to 49 years, to 16.3% (95% CI: -8.7 to 35.5) for the age group 50 to 64 years (certainty of evidence not assessed). Recombinant HA IIVs may or may not result in an increase in SAEs compared with standard IIVs, with a RR of 3.04 (95% CI: 0.32 to 29.10) based on two RCTs in adult populations aged from 18 to 64 years (low certainty of evidence). There was no significant difference reported for systemic or local adverse events observed with RIIVs compared with standard IIVs.

4.6.2 Applicability of results to adults aged 65 years and older

For MF-59® aIIVs and HD-IIVs, the findings of the updated review could be largely considered applicable to the population of interest in this HTA, that is, adults aged 65 years and older. For VE against laboratory-confirmed influenza, four out of seven NRSIs involving MF-59® aIIVs and the single RCT involving HD-IIVs were in adults aged 65 years and older. For laboratory-confirmed influenza-related hospitalisations,

the single NRSI involving MF-59® aIIVs and the single NRSI involving HD-IIVs were in adults aged 65 years and older. For SAEs, the three RCTs involving MF-59® aIIVs were in adults aged 65 years and older, while three out of six of the RCTs involving HD-IIVs were in adults aged 65 years and older, and no study included adults aged below 50 years.

For ccIIVs and RIIVs, it is unclear if the findings of the updated review can be considered applicable to adults aged 65 years and older. For vaccine effectiveness against laboratory-confirmed influenza, only one NRSI involving ccIIVs reported a sub-group analysis in patients aged 65 years and older. The second NRSI for this outcome included participants aged 4 to 64 years. For influenza-related hospitalisations and for SAEs, study populations involving ccIIVs were in adults aged 18 years and older and 50 years and older, respectively, and did not provide disaggregated results for those aged 65 years and older. For RIIVs, the majority of studies included adults aged 18 years and older and did not report disaggregated data for the cohort of interest to this HTA. However, it is noted that additional subgroup analysis was available in relation to laboratory-confirmed influenza which highlighted that when disaggregated by age, the effect was not statistically significant in those aged 65 years and older.

Almost all studies included in the updated review were undertaken in high-income countries with the majority undertaken in the US and Europe. As such, the findings were considered broadly applicable to the population in Ireland.

4.6.3 Strengths and limitations

This assessment of the efficacy, effectiveness and safety of the enhanced IIVs is based on evidence derived from an update to a systematic review published by the ECDC in March 2024. It is noted that the inclusion criteria of the updated review were more restrictive than that of the primary review, excluding outcomes that were not laboratory-confirmed (with the exception of influenza-like-illness) and study designs that did not include comparators for both safety and effectiveness outcomes. The rationale for this change was evidence that non-randomised studies which do not use laboratory-confirmed outcomes to study vaccine effectiveness may be prone to healthy vaccine bias as well as confounding by indication. As a result, only 42 of the 110 studies originally included in the primary review were considered eligible for the updated review. The updated review identified 17 new studies, so that a total of 59 studies were included in the update, of which 17 studies related to efficacy and or effectiveness data and 42 reported safety data. According to the authors of the updated review, the tighter inclusion criteria resulted in an improvement in the overall risk of bias quality assessment for the included NRSIs, compared with the primary review. In particular, risk of bias from confounding in such studies was lower than in the primary review. After quality appraisal with the

AMSTAR 2 tool, the updated review was deemed to be of high quality, as no critical or non-critical methodological weakness were identified.

Overall, the body of evidence for the efficacy and effectiveness of the enhanced IIVs remains limited. No efficacy and or effectiveness data were identified for head-to-head comparisons between enhanced IIVs. No studies investigating efficacy, effectiveness or safety of mRNA-based vaccines were identified. No data were available for vaccine efficacy and or effectiveness against influenza-related death for any of the enhanced IIVs. Available evidence were assessed as being of low to moderate certainty. Sub-group analyses (for example, based on population characteristics such as age group, pregnancy status and comorbidities) were not performed due to lack of data. For each of the enhanced IIVs, relative efficacy and or effectiveness data were reported compared with standard IIVs. The absence of head-to-head data for the enhanced IIVs makes it challenging to reliably compare between them. This can be illustrated by the following example. In the included studies comparing aIIV to standard IIV, the risk of adverse events in the comparator arm was 9.8% for headache, 2.8% for fever, 13.5% for pain and 2.2% for swelling. In contrast, for the trials comparing HD-IIV to standard IIV, the risk of adverse events in the comparator arm was 15.1% for headache, 1.7% for fever, 31.6% for pain and 5.4% for swelling. The differences in risk were all statistically significant. The sample sizes for both comparisons were in excess of 4,000 participants, therefore this difference in the risk of events suggests that either the populations or the methods of recording adverse events were systematically different between trials of the two interventions (that is, aIIV and HD-IIV). As a consequence of this, we have increased uncertainty about the relative benefits of the two enhanced IIVs.

For two of the enhanced IIVs (that is, aIIV and HD-IIV), based on the findings of the updated review, there is evidence of increased clinical effectiveness relative to standard IIVs in those aged 65 years and older. As these estimates informed the economic evaluation (Chapter 6), it is important to acknowledge the limitations of the studies from which these estimates were obtained. For both vaccine types, the estimates underpinning statistically significant effects were based on the findings of single studies. In the case of HD-IIVs, the evidence for a reduction in laboratory-confirmed influenza cases was based on a single, industry-funded RCT of 31,989 participants aged 65 years and older.[177] For the effectiveness of aIIVs in reducing hospitalisations associated with laboratory-confirmed influenza, the evidence came from a single observational study of 512 vaccinated adults aged 65 years and older.[160] The authors of this latter study acknowledged that the analysis may have been underpowered to establish rVE, which may explain the wide confidence intervals observed.

In both cases, the underlying studies collected data over two consecutive seasons. In the context of influenza, where there may be a mismatch between the

administered vaccines and the circulating strains, there can be substantial variability in vaccine effectiveness across seasons. Where the available data cover one or a small number of seasons, and or if there were differences in matching between seasons, they may be misrepresentative of the long-run 'on average' effectiveness of vaccination. While the studies available for both vaccine types are limited, it represents the best available evidence. Any conclusions on the effectiveness of these vaccines must recognise the uncertainty regarding clinical effectiveness.

A possible limitation of the tighter inclusion criteria of the updated review could be that it resulted in the exclusion of studies for some of these outcomes for which limited or no information was identified. For example, in the primary review (which included a sub-group analysis for those aged 65 years and older) the pooled RR for two of the safety outcomes were highest in the sub-group aged 65 years and older. There was a significantly increased risk of vomiting following vaccination with aIIVs compared with standard IIVs (RR 1.48, 95% CI 1.10 to 1.98). Additionally, the review identified a significantly increased risk of combined systemic effects following vaccination with HD-IIVs compared with standard IIVs (RR 1.19, 95% CI 1.09 to 1.31). While noting these differences, overall, a large evidence base is available on safety that demonstrates the safety profile of the enhanced IIVs is largely similar to that of the standard IIVs with no increased risk of SAEs detected. The aIIV, HD-IIV and RIIV were associated with an increased frequency of a number of local and systemic adverse events. This increased reactogenicity is not unexpected given the composition of these vaccines, specifically dosage differences and the use of an adjuvant. These adverse events are noted to be generally self-limiting and transient in their presentation.[10, 138]

A post-marketing survey assessment of the safety of aIIVs and HD-IIVs among adults aged 65 years and older in Australia was published in 2020.[212]. This consisted of a messaging-service based survey of self-reported adverse events following immunisation for 50,134 respondents who received an influenza vaccine in 2018. The majority (94.4%) of respondents received either an aIIV (n=28,003) or a HD-IIV (n=19,306). The authors noted that adverse events were more commonly reported by individuals who received a HD-IIV than for other influenza vaccines. However, this difference was small after adjustment for potential confounders, and reports largely consisted of non-serious events. The rates of medical care seeking behaviour were low and did not differ between the two enhanced vaccine groups, indicating no unexpected burden on the healthcare system due to adverse events associated with influenza vaccines. Additional post-marketing surveillance reports for HD-IIVs in the US,[213] and aIIVs in Italy,[214] did not reveal any new safety concerns. Continued postmarketing surveillance is important to understand the benefits and risks of the enhanced influenza vaccines.

The absence of sub-group analyses by age in the updated review, in particular in adults aged 65 years and older, may limit the applicability of some of the findings of the updated review to this HTA. In reporting the findings of the updated review, evidence of vaccine effectiveness from studies conducted in those aged 65 years and older was highlighted. Considering evidence of vaccine safety, where possible, the number of studies specific to the population aged 65 years and older were highlighted, including the proportion of all participants that they represented and weighting the participants had in the random-effects meta-analyses. Since it has been demonstrated that the effectiveness of influenza vaccines is generally higher in younger adults compared with older adults, it is important that studies assess the efficacy and or effectiveness and safety of enhanced IIVs in older adults specifically. Finally, another limitation of this analysis is the reliance on international evidence where there may be inconsistency in the definitions used. For example, in a systematic review of the methods used to estimate rVE in influenza, the authors reported substantial variation in the definitions and approaches employed across the included studies and concluded that rVE studies should be better described to include the definition of rVE used.[215]

It is noted that the systematic review considered the relative efficacy and or effectiveness of enhanced IIVs compared with standard IIVs. An estimate of the effectiveness of the standard IIVs was therefore also required to inform the epidemiological model (Chapter 6). This estimate was informed by published data from the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) groups in Europe which consider the effectiveness of influenza vaccination relative to no vaccination. As noted in Section 4.2.1, these data potentially include studies where enhanced vaccines were also used and as such may overestimate the effectiveness of standard IIVs in the adult population, particularly in those aged 65 years and older. However, the included data relate to influenza seasons from 2008-2009 to 2019-2020 and as such generally pre-date the widespread availability of the enhanced vaccines, the first of which was authorised by the EMA in 2018. Moreover, where reported, enhanced vaccines accounted for a small minority of vaccine use in the included study populations. As such, the pooled estimates are considered a broadly accurate reflection of the effectiveness of standard influenza vaccines.

4.6.4 Conclusion

The primary review concluded that the evidence base for the efficacy and or effectiveness of enhanced IIVs was limited. The updated review concluded that this evidence base is still limited. The evidence base demonstrated an overall safety profile that was similar for enhanced IIVs and standard IIVs with respect to SAEs, although the certainty in this evidence was low. There were however differences

observed in systemic and local adverse effects between enhanced IIVs and standard IIVs, with a significantly increased risk of these effects reported with aIIVs, HD-IIVs and ccIIVs.

As sub-group analyses were not performed, the updated review did not comment on the applicability of these findings specifically to adults aged 65 years and older. For aIIVs and HD-IIVs, evidence was available for the efficacy and or effectiveness and safety outcomes in adults aged 65 years and older, increasing the applicability of these findings to this age group. For ccIIVs and RIIVs, studies were largely in mixed adult populations with very limited evidence specific to adults aged 65 years and older.

5 Review of methodology for economic modelling studies of inactivated influenza vaccinations

Key points

- The most recent systematic review of economic modelling studies of seasonal influenza vaccination in high-income countries was published in 2022, based on a literature search conducted up to 2020.
- To establish and assess the most up-to-date international evidence on the approaches taken to the economic modelling of vaccination with an inactivated influenza vaccine (IIV) in adults aged 65 years and older, a rapid review of studies published since 2020 was undertaken.
- Nineteen additional studies were identified in the rapid review, 15 of which were conducted within EU/EEA countries. Fifteen of the included studies were industry funded, three were conducted using government research funding and one study received EU funding.
- The primary differences in methodological approach related to whether a single cohort or multiple cohorts were modelled, in addition to the type of model chosen.
- To estimate the impact of vaccination, 10 studies used static decision tree Markov models, seven studies incorporated decision tree economic models with dynamic transmission models, one study used a state transmission simulation model, and one study described the model used as a static decision analytic model (but did not specify the model type).
- The majority of the studies conducted their analysis over a short time horizon of one year or less. There was variation in the values of absolute vaccine effectiveness (VE) against influenza used across studies, though greater consistency was observed where relative vaccine effectiveness (rVE) values were used, which is most likely due to the lack of high-quality studies conducted in this area.
- Seven studies adopted a dual perspective (considering both the healthcare and societal perspective) in the base-case analysis when evaluating the cost-effectiveness of vaccination strategies, while eight studies conducted their analysis from a healthcare perspective only. A further two studies adopted a societal perspective in the base-case analysis, and also included a scenario

analysis from the perspective of the payer. Two studies did not clearly report the perspective taken when assessing the impact of vaccination.

- The appraisal of included studies highlighted some concerns with regards to the structure, data and consistency of the models. In some studies, static models were chosen to model mixed cohorts, when dynamic transmission models would have been a more appropriate choice. Uncertainty was often not sufficiently addressed, in particular structural and methodological uncertainty. Across studies, both methods of identifying data and the level of detail provided for parameter data were poorly reported, particularly in relation to vaccine effectiveness estimates and estimated quality-adjusted life years (QALYs) lost.
- This rapid review identified several notable modelling features for consideration when developing an economic model of universal vaccination with an enhanced IIV in adults aged 65 years and older, all of which will be considered in the development of a de novo economic model for Ireland.

5.1 Introduction

This chapter reviews published international economic evaluations of seasonal influenza vaccinations. The review specifically examines the approaches taken to modelling the expected costs and benefits of vaccination with an inactivated influenza vaccine (IIV) in those aged 65 years and older. The findings of this review will inform the development of a de novo economic model to assess the cost effectiveness of universal vaccination with an enhanced IIV in those aged 65 years and older in Ireland.

5.2 Background

A total of 13 different considerations have been identified for modelling economic evaluations of vaccination programmes specifically. These include:

- model selection
- time horizon of models
- natural disease history
- measures of vaccine-induced protection
- duration of vaccine-induced protection
- indirect effects apart from community protection
- target population
- model calibration and validation
- handling uncertainty
- discounting

- health-related quality of life
- cost components
- perspective adopted.[216]

A scoping exercise was undertaken to identify published systematic reviews of economic evaluations of influenza vaccination in older adults (age 65 years and older) that provide detail on the economic models employed and the model input parameters. Three systematic reviews were identified, with heterogeneity observed in a number of aspects of the economic evaluations, including the perspective adopted, type of model, assessment of indirect costs, and estimation of the efficacy parameters.[217-219]

The most recent systematic review, published in 2022 and comprising a search of MEDLINE, JBI Evidence-Based Practice Database, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials up to 29 October 2020, assessed the cost effectiveness of routine influenza vaccination estimated by modelling studies.[219] The review included 27 studies that evaluated the cost effectiveness of influenza vaccination in older adults and provided relevant data on the type of model employed, model input parameters, vaccine characteristics and economic results.

In order to establish the most up-to-date evidence of the models employed and parameters used for the economic evaluation of influenza vaccination, a rapid review was conducted. The rapid review sought to identify economic evaluations of influenza vaccination that have been published since 2020 (to cover the last search date for the most recent systematic review) to July 2023.

5.3 Rapid review methods

5.3.1 Research question

Research question: What approaches have been used to model the expected costs and benefits of vaccination with an IIV in those aged 65 years and older?

See Table 5.1 for the Population, Interest, Context (PICo) framework that was developed to address the above research question.

Table 5.1 PICo for rapid review of economic evaluations of vaccination with an inactivated influenza vaccine in those aged 65 years and older

Population	Adults aged 65 years and older receiving an inactivated influenza vaccination.*
Interest	Approaches to modelling the expected costs and benefits of vaccination with an inactivated influenza vaccine, including, but not limited to: ▪ model structure ▪ model input parameters ▪ model outputs.
Context	Vaccination with an inactivated influenza vaccine in those aged 65 years and older (or that included a subgroup consisting of those aged 65 years and older) in high-income countries.‡

*Inactivated influenza vaccines (IIVs) included standard and enhanced IIVs (both trivalent and quadrivalent). Enhanced IIVs are those that have been modified to overcome reduced vaccine effectiveness, through adaptations to the vaccine structure, composition or dosage (to include adjuvanted, high-dose, cell-based and recombinant influenza vaccines).
‡As defined by the OECD: WDI - The World by Income and Region (worldbank.org)

5.3.2 Eligibility criteria

The following studies were eligible for inclusion: economic modelling studies of vaccination with an IIV in those aged 65 years and older (or included a subgroup consisting of those aged 65 years and older) in high-income countries that describe the approach to modelling, provide detail on the model structure and model input parameters, include both costs and outcomes in the analysis and report a ratio of (incremental) costs to (incremental) benefits.

5.3.3 Search strategy

A comprehensive electronic search was conducted in Medline Complete via EBSCOhost, Embase via Ovid, CINAHL via EBSCOhost, The Cochrane Library and INAHTA database from 1 January 2020 to 23 July 2023. A forward citation search of the most recent systematic review[219] and the studies included from the electronic database search was also undertaken. No language restrictions were applied. The database search strings, developed in consultation with a librarian, dates of searches and search results are provided in Appendix A5.1.

5.3.4 Study selection and data management

Results were exported to Covidence software and screened by one reviewer for relevance.[220] The full texts of potentially eligible articles were retrieved and independently assessed for eligibility by two reviewers according to the pre-specified inclusion and exclusion criteria outlined in Table 5.1 and Section 5.3.2. Any uncertainty with screening or inclusions was resolved through discussion or, if necessary, involvement of a third reviewer.

5.3.5 Data extraction and quality appraisal

Table 5.2 details the data that were extracted for each included study. Data extraction for each study was conducted by one reviewer using a standardised, pre-piloted electronic data extraction form and checked by a second reviewer. In line with the systematic review being updated,[219] critical appraisal of all included studies was undertaken using the framework for quality assessment of decision-analytic models proposed by Philips et al..[221] The framework assesses the quality of models under three key themes, *Structure, Data and Consistency*. Quality appraisal was conducted by one reviewer and checked by a second. Disagreements in data extraction and quality appraisal were resolved through discussion or, if necessary, involvement of a third reviewer. All incremental cost-effectiveness ratio (ICER) values were extracted as reported by the study authors at time of publication, with no adjustments made for inflation, and no currency conversions carried out.

Table 5.2 Data extracted from each included study, where available

General study characteristics	▪ author name ▪ year of publication ▪ country ▪ type of economic evaluation ▪ population ▪ funding source
Model characteristics	▪ model type (for example, static decision tree, dynamic transmission) ▪ perspective ▪ time horizon ▪ comparator (standard inactivated influenza vaccine) ▪ discount rates for costs and outcomes ▪ sensitivity analysis
Intervention and vaccination strategy	▪ vaccine type (adjuvanted, cell-based, recombinant, high-dose) ▪ age at vaccination ▪ dosing schedule ▪ coverage rate
Vaccine characteristics	▪ efficacy or effectiveness ▪ waning of immunity
Direct costs	▪ type of costs included ▪ methods of measurement and valuation
Indirect costs	
Direct effects including long-term effects	▪ type of effects included ▪ methods of measurement and valuation
Indirect effects	
Economic results	▪ type of summary ratio ▪ overall healthcare perspective result ▪ overall societal perspective result ▪ authors' conclusions

5.3.6 Data synthesis

Summary characteristics of included studies and the vaccination strategies and vaccine characteristics considered in the models are presented in table format. The reporting of this review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.[222]

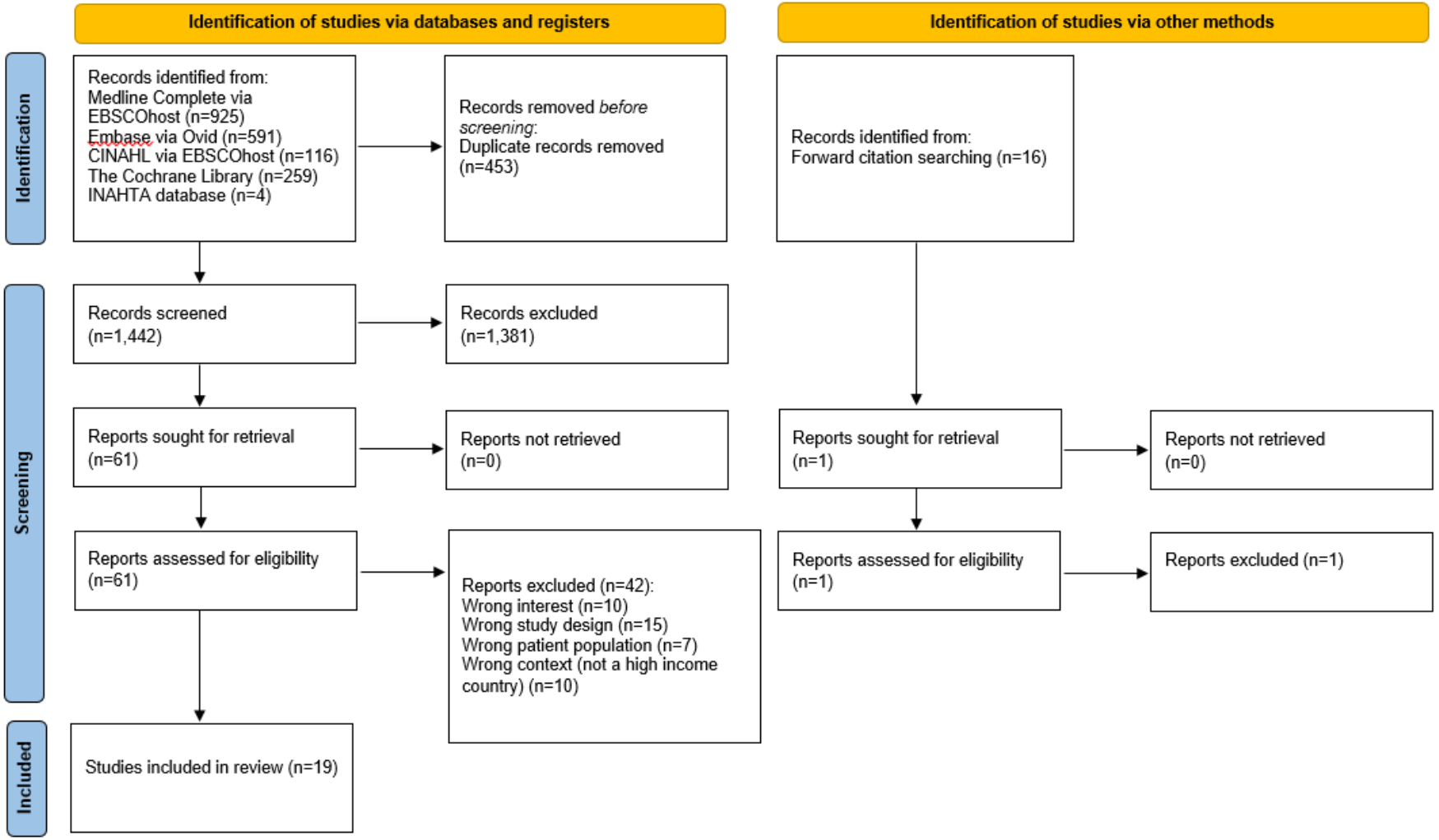
5.4 Results

A total of 1,895 articles were identified in the database searches. Following the removal of duplicates, 1,442 articles remained. Sixteen additional articles were identified through forward citation searching. All articles were screened by title and abstract; after exclusions, a total of 61 articles remained for full-text review. Following full-text review and subsequent exclusion, 19 studies were included (Figure 6.1). Full data extraction tables for included studies are provided in Appendix A5.2.

5.4.1 Characteristics of included studies

A total of 19 model-based studies met the inclusion criteria for this rapid review. Of these, one was published in 2020,[223] four were published in 2021,[224-227] eight were published in 2022[228-235] and six were published in 2023.[236-241] Fifteen studies were conducted in EU/EEA countries, five of which included multiple countries or regions in their analysis. Of these five multi-centre studies, two included Belgium, Finland and Portugal,[237, 240] one included Denmark, Norway and Sweden,[239] one included England and Wales,[225] and one included England, France, Ireland, the Netherlands, Portugal, Scotland, Spain and Navarre (Spain).[235] The remaining 10 EU/EEA studies were conducted from a single country perspective, with five in Spain[223, 224, 229, 232, 241] and one each in the UK,[226] Germany,[231] Ireland,[236] Italy[227] and Portugal.[228] Four studies were conducted in other regions, one in the US,[238] one in Canada,[230] one in Uruguay[234] and one in South Korea.[233] An overview of the general study characteristics and model characteristics is provided in Table 5.3. All 19 studies were conducted as cost-utility analyses (CUAs) using quality-adjusted life year (QALY) health effects, with four studies also presenting cost-effectiveness analyses (CEAs) in terms of life years gained.[227, 234, 237, 240] Fifteen of the included studies were funded by industry, with three studies reporting funding from government research funds[228, 233, 238] and one study received EU funding.[235]

Figure 5.1 PRISMA flow diagram of included studies



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 5.3 General study characteristics of included studies

Study	Year	Country/ Region	Model type	Time horizon	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
Alvarez[240]	2023	Belgium Finland Portugal	Static decision-tree model	Average influenza season	CUA CEA	Total payer (including patient co-payment): Belgium/Finland NHS: Portugal	Belgium: 1.5% Finland: 3% Portugal: 4%	Industry
Bianculli[234]	2022	Uruguay	Static decision analytic model	Average flu season	CUA	Direct health costs Societal	3%	Industry
Choi[233]	2022	South Korea	Static decision-tree model	One year	CUA	Healthcare sector Societal	4.5%	Government
Crepey[223]	2020	Spain	Dynamic transmission model and decision-tree model	Not clear	CUA	Public healthcare system Societal	3%	Industry
Fochesato[232]	2022	Spain	Dynamic transmission model and decision-tree model	Not clear	CUA	Public healthcare system Societal	3%	Industry
Jacob[239]	2023	Denmark Norway Sweden	Static decision-tree model	One influenza season	CUA	Healthcare sector Societal	Denmark: 3.5% Norway: 4% Sweden: 3%	Industry
Kim De Luca[238]	2023	US	State transition simulation model	One year	CUA	Societal Healthcare sector (scenario)	3%	Government
Kohli[226]	2021	UK	Dynamic transmission model and decision-tree model	10 influenza seasons (results of analyses presented as average annual outcomes)	CUA	Public healthcare sector: NHS and personal social services	3.5%	Industry

Study	Year	Country/ Region	Model type	Time horizon	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
Kohli[231]	2022	Germany	Dynamic transmission model and decision-tree model	10 influenza seasons (results of analyses presented as average annual outcomes)	CUA	Societal Social health insurance (scenario)	3%	Industry
Marbaix[237]	2023	Belgium Finland Portugal	Static decision-tree model	One year	CUA CEA	National healthcare payer perspective	1.5%	Industry
Mattock[225]	2021	England and Wales	Static decision-tree model	One influenza season	CUA	Healthcare sector: NHS and prescribed specialised services	3.5%	Industry
Nguyen[230]	2022	Canada	Dynamic transmission model and decision-tree model	8 years	CUA	Not clear	5%	Industry
Nguyen[236]	2023	Ireland	Dynamic transmission model and decision-tree model	Not clear	CUA	Healthcare sector Societal	3%	Industry
Redondo[224]	2021	Spain	Static decision-tree model	6 months	CUA	Healthcare system	3%	Industry
Ruiz-Aragón[229]	2022	Spain	Static decision-tree model	One year	CUA	Direct medical payer Societal	3%	Industry
Ruiz-Aragón[241]	2023	Spain	Static decision-tree model	One year	CUA	Not clear	3%	Industry
Rumi[227]	2021	Italy	Static decision-tree model	One year	CUA CEA	Healthcare sector: NHS	3%	Industry

Study	Year	Country/ Region	Model type	Time horizon	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
Sandmann[235]	2022	England France Ireland The Netherlands Portugal Scotland Spain Navarre (Spain)	Dynamic transmission model and decision-tree model	One year	CUA	Healthcare sector	3%	EU funding
Tavares[228]	2022	Portugal	Static decision-tree model	One year	CUA	Healthcare sector: NHS	None applied	Research/ Government

Key: CBA – cost-benefit analysis; CEA – cost-effectiveness analysis; CUA – cost-utility analysis; EU – European Union; NHS – National Health Service.

5.4.2 Model characteristics of included studies

Model

Static decision-tree models were used in ten studies,[224, 225, 227-229, 233, 234, 237, 239-242] seven studies incorporated decision tree economic models with a dynamic transmission model,[223, 226, 230-232, 235, 236] one study used a state transmission simulation model,[238] and one study described the model used as a static decision analytic model without clearly specifying which type (however, from diagrammatic representation, it was assumed to be a static decision-tree model).[234] The study that incorporated a state transmission simulation model omitted details of cycle length and did not specify discrete time or discrete event simulation.[238] Only one study that used a dynamic transmission model recorded details of a time step, although the stated time step did not align with the original model referenced.[231] Nine of the included studies provided rationale for model choice,[223, 224, 226, 229, 230, 232, 234, 240, 241] four of which used a dynamic transmission model incorporating the effects of vaccination strategies modelled in the entire population,[223, 226, 230, 232] and five of which used a static model where populations were either limited to those aged 65 years and older,[224, 229, 240, 241] or limited to populations considered at increased risk of disease only.[234] Irrespective of model type, the economic evaluations all comprised pathways or health states as measured by health resource usage. These include some or all of the following:

- vaccination/no vaccination
- influenza (symptomatic/influenza-like-illness/laboratory-confirmed influenza)
- general practitioner/primary care visit, emergency department (ED) visit, hospitalisation
- death from influenza or other causes/alive.

Some models included complications as part of inpatient or outpatient pathways while one study included intensive care resource usage for complications.

Time horizon

A short time horizon of between six months and one year was used in 13 studies. These included three studies which reported a six-month time horizon,[224, 239, 240] with two of these equating this to an average or single flu season.[239, 240] Two further studies reported a time horizon over a single or average influenza season without specifying the length.[225, 234] Eight studies reported over a one-year time horizon.[227-229, 233, 235, 237, 238, 241] One study reported over an eight-year time horizon.[230] Two studies used a time horizon over 10 influenza seasons, but reported an average annual result.[226, 231] Three studies did not clearly report the time horizon used.[223, 232, 236] Eleven studies also reported either associated costs or

effects of premature influenza-related mortality over a longer and or lifetime horizon.[224, 225, 227, 229, 233, 234, 237-241]

Perspective

Dual perspectives (payer and societal) were considered in seven studies as part of the base-case analysis.[223, 229, 232-234, 236, 239] Two studies reported from the societal perspective as the base case, but included other perspectives in the scenario analyses.[231, 238] One US study included the healthcare sector perspective as a scenario analysis,[238] while one German study included the social health insurance perspective as a scenario analysis.[231] Two studies did not explicitly state the perspective of the analysis,[230, 241] although assumptions based on parameter inputs included would suggest a healthcare perspective[230] and a societal perspective were used.[241] In terms of base-case payer perspectives taken, most included direct medical costs to national healthcare system payers,[223-229, 232-237, 239, 240] while patient co-payments were included in the base-case analysis in one study[240] and as a part of a scenario analysis in another study.[237]

Discount rates

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Accordingly, any costs or outcomes occurring beyond one year should be discounted using standard methods. The majority of studies conducted their analysis over a short time horizon of one year or less. As such, any direct costs related to vaccination or complications of influenza within this period were not subject to a discount rate. Five studies included costs related to long-term outcomes; accordingly, these were subject to discounting. These long-term outcomes were productivity losses over a lifetime horizon,[229, 241] costs associated with death and long-term sequelae of influenza,[238] productivity losses[233] and indirect costs associated with premature death.[232]

Studies which included the above costs applied the same discount rates to both costs and outcomes. A variety of discount rates was applied across the studies, including 1.5% in Belgium;[237, 240] 3% in Finland,[240] Uruguay,[234] Spain,[223, 224, 229, 232, 241] Sweden,[239] the US,[238] Germany,[231] Ireland[236] and Italy;[227] 3.5% in Denmark[239] and the UK;[225, 226] 4% in Portugal[240] and Norway;[239] 4.5% in South Korea[233] and 5% in Canada.[230] Sandmann et al.[235] applied a 3% discount rate after the first year to a range of different country scenarios as per the World Health Organization (WHO)-CHOICE recommendations.[243] One study did not report a discount rate, and did not reference discounting in their analysis.[228]

Studies were not always clear which outcomes were followed beyond the time horizon of the model, and few studies reported discounting of effects unrelated to

premature mortality. One study reported that QALYs associated with long-term sequelae were discounted,[238] while another specifically reported that QALYs accrued after the first year were discounted.[232] Two studies reported discounting of productivity and QALY losses over a lifetime horizon,[229, 241] while one further study reported applying a discount rate to outcomes over a lifetime horizon.[227] Three studies conducted their analysis over multiple influenza seasons, but the time horizon over which effects were followed, and thus discounted, was not explicitly clear.[226, 230, 231] One study carried out over eight seasons reported that all QALY losses were discounted, but did not clearly specify whether QALY loss represented an average figure for each season, or whether outcomes were followed over a longer time horizon.[230] Two further studies which conducted analyses over a 10-year time horizon only reported average discounted QALYs per season, with no further information provided.[226, 231]

5.4.3 Intervention and vaccination strategies

A number of different vaccination strategies were assessed in the models (Table 5.4). Adjuvanted quadrivalent influenza vaccine (aQIV) was the most frequently assessed enhanced IIV, representing the intervention in the base-case analysis in seven studies, where it was compared with a standard QIV in four studies[231, 232, 237, 239] and compared with high-dose quadrivalent influenza vaccine (HD-QIV) in five studies.[226, 229, 231, 237, 239] One study also compared aQIV to a standard QIV in adults aged 65 years and older as part of a combined vaccination programme, where it was assessed alongside quadrivalent live attenuated influenza vaccine (QLAIV) as an intervention in children aged 2-17 years and alongside a standard QIV in at-risk adults under 65 years of age.[236] One additional study conducted a scenario analysis comparing aQIV with no vaccination in adults aged 65 years and older.[238]

Three studies assessed HD-QIV as the intervention in the base-case analysis, of which two studies compared HD-QIV with standard QIV,[227, 240] and one study compared HD-QIV with standard trivalent influenza vaccine (TIV).[233] HD-QIV was also assessed as part of a combined vaccination programme in a Canadian study, where one programme (which consisted of using a HD-QIV in adults aged 65 years and older and a standard QIV in individuals aged between six months and 64 years) was compared with a second programme (which consisted of using a standard QIV in all individuals aged over six months.[230] Two studies also included HD-QIV in threshold scenario analyses, which aimed to determine acceptable prices for HD-QIV over a range of relative vaccine effectiveness scenarios, one of which compared HD-QIV with aQIV,[226] while the other study compared HD-QIV with (i) with any vaccine and (ii) with no vaccination in adults aged 65 years and older.[238]

Only one study assessed the cost effectiveness of recombinant QIV (RIV4) in the base-case analysis, where it was compared with aQIV.[238] RIV4 was also assessed as part of a US study which performed a threshold analysis of vaccine effectiveness and cost in adults aged 65 years and older, where RIV4 was compared with no vaccination.[238]

A number of studies assessed enhanced trivalent influenza vaccines (TIVs) as the intervention against various comparators. One study assessed the cost effectiveness of high-dose TIV (HD-TIV) compared with adjuvanted TIV (aTIV) in England and Wales.[225] Sandmann et al. conducted a large scale modelling study across eight EU/EEA countries and or regions and assessed the cost effectiveness of an enhanced TIV (either aTIV or HD-TIV) compared with standard TIV in adults aged 65 years and older.[235] Sandmann et al. also conducted an analysis which compared a combined vaccination strategy (that is, the use of an enhanced TIV in adults aged 65 years and older in conjunction with mass paediatric vaccination with either a standard TIV or standard QIV with a second programme (that assessed the use of a standard TIV in adults aged 65 years and older only).[235] An aTIV was also assessed as part of a combined intervention by Choi et al.,[233] as mentioned above, and by Nguyen et al. (2022), who assessed aTIV in two strategies; aTIV in adults aged 65 years and older in conjunction with either (i) a standard, egg-based QIV or (ii) a cell-based QIV (ccQIV) in those aged under 65 years, compared with a standard, egg-based QIV at all ages.[230]

A standard QIV was assessed as the intervention in four studies compared with a standard TIV,[223, 228, 234, 235] and as part of combined programmes in two studies.[233, 235] Choi et al. assessed the cost-effectiveness of two combined vaccine programmes in South Korea where one programme (which combined a standard QIV in adults aged 65 years and older and an aTIV in both at-risk adults and those aged 50 to 64 years) was compared with a second programme (which combined a standard TIV in adults aged 65 years and older and either a standard TIV or a standard QIV in at-risk adults and those aged 50-64 years).[233] Sandmann et al. also assessed the cost effectiveness of a standard QIV as part of a combined vaccination programme targeting children aged four to 16 years and adults aged 65 years and older. Two of the five strategies assessed switching from a standard TIV to either (i) standard QIV or (ii) an 'improved' TIV (that is, either aTIV or HD-TIV) in adults aged 65 years and older, in addition to mass paediatric vaccination with either a standard QIV or standard TIV.[235]

Details of dosing schedules were omitted from all but one multi-cohort US study, which specified that previously non-vaccinated children were to receive two doses.[238] Though not explicitly stated, it can be assumed that the remaining included studies modelled the administration of one dose of an influenza vaccine per

individual per influenza season. The age at vaccination in the studies aligned with the study populations being targeted. Nine studies focused purely on populations aged 65 years and older, with all individuals in this group eligible for vaccination.[224, 225, 227-229, 237, 239-241] Three studies included populations aged less than 65 years of age at high risk of complications from influenza,[223, 233, 234] and ten studies investigated multiple cohorts.[223, 226, 230-236, 238] See Table 5.4 for more information.

5.4.4 Vaccine characteristics

Vaccine effectiveness (VE) was reported in different ways across the included studies (Table 5.4). Seven studies reported figures for VE against influenza overall,[225, 227, 228, 233, 236-238] nine studies reported VE against a specific strain of influenza (for example, A strain, AH1N1, AH3N2, B strain, B Victoria, B Yamagata),[223, 224, 230-232, 234, 235, 239, 240] while 13 studies reported relative vaccine effectiveness (rVE) estimates.[224-227, 229-232, 235, 236, 239-241] Only two studies reported cross protection of vaccines against mismatched B strains.[223, 234]

VE against influenza (overall)

Seven studies use values for absolute VE against influenza in their model.[225, 227, 228, 233, 236-238] Five of the seven studies[227, 228, 233, 236, 237] provided estimates for VE of standard dose QIV versus influenza (between 14.6%[227] and 64.2%[233]), and two of these studies also provided estimates for VE of standard TIV versus influenza of 58%[233] and 59%.[228]

Tavares et al.[228] used standard TIV vaccine efficacy data based on a 2018 Cochrane review,[244] which considered VE in those aged 65 years and older. This rate was adjusted using Portuguese influenza data to apply a rVE of 3.3% to represent the increased efficacy of standard QIV on circulating B strains.[228] This Cochrane review[244] was also cited by Choi et al.,[233] who derived a value for VE of TIV using the data from both this review[244] and a second 2018 Cochrane review, which was based on a healthy adult population.[245] The authors then applied a rVE of standard QIV relative to standard TIV of 5.2%, based on the assumption of increased VE against mismatched B strains, [233, 246, 247] which resulted in VE values of 59% for standard TIV and 64.2% for standard QIV for those aged less than 65 years (both high and low risk).[233] The authors also reported VE values for both standard TIV (58%) and standard QIV (63.2%) in those aged 65 years and older.[233]

Marbaix et al. use a value for VE of standard QIV versus no vaccination (40.2%),[237] which was estimated using efficacy data from a meta-analysis conducted by Belongia et al.[248] alongside Belgian influenza surveillance data detailing strain distribution in older people (age not specified).[249] Nguyen et al. (2023) reported

age-specific VE figures for standard QIV based on UK influenza vaccine GP surveillance data which ranged from 45.3% to 54% in those aged under 64 years, and 45.4% to 47.8% in those aged 65 years and older.[236]

Mattock et al.[225] reported the VE of standard QIV versus no vaccination as 46% against laboratory-confirmed influenza incidence,[250] 28% against mismatched B laboratory confirmed influenza[251] and 28% against hospitalisation;[251] these values were derived from UK observational reports and previous cost-effectiveness studies.[225] Rumi et al.[227] reported a VE value for standard QIV for absolute efficacy at preventing cardiorespiratory hospitalisation versus no vaccination, citing another cost-effectiveness analysis as the source of the estimate.[242]

Only one US study compared vaccination with any vaccine with no vaccination and reported age-specific VE figures, calculated using data from the US Flu Vaccine Effectiveness network.[238] VE values ranged from 27% in adults aged 65 years and older to 46% in children aged six months to four years.[238]

VE against influenza (strain specific)

Four studies used values for absolute VE against influenza A,[224, 234, 235, 240] with reported values ranging from 23.8%[240] to 61%,[234] with little consistency in the sources cited. Nine studies which reported a VE against influenza B also reported a wide range of values,[223, 224, 226, 230, 232, 234, 235, 239, 240] from 9%[230] to 80%.[223]

Bianculli et al.[234] used an age group specific standard TIV efficacy rate of 51% to 61% against A strain, of 66% to 77% against matched B strain, and of 44% to 52% against mismatched B strain, citing a cost-effectiveness analysis conducted in the US.[252] Sandmann et al.[235] reported overall VE of standard TIV by season, age group, and influenza subtype based on ECDC estimates and published literature.[248] Redondo et al.[224] used a VE of standard TIV against influenza A and B (matched) of 50%, sourced from a RCT conducted in an elderly population,[253] and mismatched (35%), sourced from a meta-analysis conducted in children and adults.[224]

Alvares et al., who conducted a multi-centre study for Finland, Portugal and Belgium, estimated the VE of standard QIV using the weighted average of effectiveness against influenza strains from country-specific vaccination reports.[240] The VE for standard QIV for Finland was sourced from data over the 2015 to 2019 influenza seasons,[240] and the VE for standard QIV for Portugal was obtained from a study by Fleming et al.,[250] whose values were obtained using community surveillance data from three consecutive influenza seasons. In the absence of Belgian data, an absolute VE for standard QIV against influenza of 50% was assumed for both A and B strains.[240]

Five studies used strain-specific VE values against influenza A in their model,[223, 226, 230, 232, 239] with values ranging between 9%[230] and 73%[232] for A(H1N1) and 9%[230] to 67%[223] for A(H3N2). Fochesato et al.[232] used age-stratified VE estimates of standard QIV against AH1N1, AH3N2 and B strain, which were drawn from a meta-analysis produced as part of an Italian HTA.[254] VE data for standard QIV by influenza strain ranging from 24% to 63% was sourced from a meta-analysis[248] conducted by Belgonia et al., which Jacob et al. then used to derive an average VE for standard QIV using strain circulation data for five seasons.[239] Kohli et al.[226] (2021) used this same meta-analysis by Belongia et al.[248] as the source of their estimates. Nguyen et al. (2022) used Canadian GP sentinel data to derive year and strain specific VE figures for standard QIV, ranging from 9% to 72%.[230] Crepey et al. reported age specific TIV VE of 41% to 67% against A strains, and 49% to 80% for B strains.[223] These values were derived from a meta-analysis[246] and adjusted for age-specific rates using unpublished US CDC figures.[223]

Cross-protection studies

Only two studies, both comparing standard QIV with standard TIV, assumed cross-protection against a mismatched B strain.[223, 234] Crepey et al. assumed a level of cross-protection of 70%,[223] citing Diaz-Granados et al. (2012),[246] a systematic review and meta-analysis of clinical trial vaccine efficacy data in children and 'non-elderly' adults. Bianculli et al. used a value of 67%,[234] citing a CEA[252] from the US which generated their own clinical efficacy data using the same systematic review,[246] in addition to other studies.[247, 255, 256]

rVE of aIIVs versus standard IIVs

Five studies reported rVE values (range: 0% to 36.9%) for aIIVs compared with standard IIVs.[224, 225, 231, 232, 236] Three[231, 232, 236] of the five studies cited a systematic review and meta-analysis conducted by Coleman et al.[257] as the source of their rVE values. This meta-analysis compared aTIV with standard TIV, and reported a rVE value of 13.9% for prevention of any medical encounter occurring as a result of influenza infection.[257] Two of the included studies[231, 236] adopted this value (13.9%) as their overall rVE value and the third study used this estimate as the rVE for prevention of influenza with or without pneumonia in an outpatient setting.[232] This third study also reported a rVE of 34.6% for prevention of laboratory-confirmed influenza,[232] which was taken from another systematic review and meta-analysis conducted by Calabro et al., comparing aTIV to standard TIV.[254]

Two of the five studies[224, 225] cited a retrospective observational study as the source of the rVE values used.[258] This study was conducted over one influenza season in Spain, and reported a rVE of 6% for aTIV compared with standard TIV.[258] Redondo et al.[224] used this rVE estimate to represent rVE of aTIV versus standard TIV

against influenza overall. Mattock et al. also used the same rVE value (6%) as part of their analysis, as one of a range of estimates of rVE for prevention of influenza-related hospitalisations (0%, 6% and 12%).[225] The upper rVE value for prevention of hospitalisation (12%) was obtained from a prospective observational study conducted in Italy.[259] Mattock et al. also used a range of estimates for laboratory-confirmed influenza (0%, 10% and 20%).[225] The upper rVE estimate for laboratory-confirmed influenza (20%) was obtained from another CEA[260] in the absence of clinical or observational evidence. Mattock et al.[225] assumed a lower rVE estimate of 0% for both prevention of laboratory-confirmed influenza and influenza-related hospitalisation in their analysis, also on the basis of this lack of evidence, with the authors citing multiple observational studies where a non-statistically significant difference was observed between aTIV and standard TIV.[261, 262] The rVE value of 10% for prevention of laboratory-confirmed influenza was chosen by the authors as it was the midpoint between 0% and 20%.[225]

Only one[232] of the three included studies which assessed quadrivalent formulations in their analysis justified extrapolation of rVE values relating to trivalent formulations to quadrivalent formulations.[231, 232, 236] Fochesato et al.[232] highlighted both the dearth of available real-world evidence relating to aQIV, and that extrapolation of values from trivalent to quadrivalent formulations was consistent with the approach taken by the European Medicines Agency (EMA).[263]

rVE of HD-IIVs versus standard IIVs

Eight studies compared HD-QIV with standard IIVs as part of their analyses, and consistency was observed with regard to the rVE estimates used across these studies (range: 17.8% to 24.3%).[224, 225, 227, 229, 233, 237, 239, 240]

All eight studies cited an RCT conducted by Diaz Granados et al. as the source of their estimate for rVE for the prevention of influenza,[177] reporting an rVE value of either 24%[229, 233] or 24.2%.[224, 225, 227, 237, 239, 240] The RCT by Diaz Granados et al. compared HD-TIV to standard TIV in adults aged 65 years and older, with assessment of efficacy and effectiveness performed over two consecutive influenza seasons in the Northern Hemisphere (2011-2012).[177] The figure of 24.2% related to laboratory-confirmed influenza. Three of the included studies justified use of this evidence where quadrivalent vaccines were assessed,[224, 227, 240] citing an immunobridging clinical trial which stated that the relative efficacy between standard TIV and standard QIV is comparable,[179] which is consistent with the approach taken by the EMA.[263]

Sandmann et al.[235] also compared a switch from standard QIV to an enhanced TIV (either aTIV or HD-TIV) in those aged 65 years and older, and used the same rVE estimate of 24.2%.[177] The authors cited the lack of studies comparing quadrivalent

and trivalent formulations and assumed the same rVE value for both aTIV and HD-TIV compared with standard QIV.[235]

Five[224, 225, 227, 229, 240] of the eight studies cited a systematic review and meta-analysis (by Lee et al.)[264] of the rVE of HD-TIV versus standard TIV against influenza-like illness. The rVE estimates reported ranged from 17.8% to 24.3%.[264]

One of the multi-centred studies[240] identified in this review used two different rVE estimates from Lee et al.,[264] 17.8% (for prevention of influenza-related hospitalisation for both Belgium and Portugal), and 24.3% (for prevention of pneumonia-related hospitalisation in Finland). The rVE value of 24.3% for prevention of pneumonia-related hospitalisation was used in two studies,[224, 225] as the figure for prevention of influenza-related hospitalisation. Another study[227] used an estimate of 18.2% (again from Lee et al.)[264] as the rVE for prevention of hospitalisation from cardiorespiratory events occurring as a result of influenza. Another study[229] cited Lee et al.[264] as the reference for relative vaccine efficacy as well as Diaz Granados,[177] rounding to a rVE of 24%.

rVE of aIIVs versus HD-IIVs

Six studies analysed aQIV compared with HD-QIV as part of their analysis,[226, 229-231, 237, 239] and all six studies referenced a systematic review and meta-analysis by Coleman et al. as the source of their estimates in some capacity.[257] This review used observational data from four studies comparing aTIV and HD-TIV, and provided an rVE value (3.2%) for the prevention of any medical encounter due to influenza and or pneumonia.[257]

Three of the included studies used this estimate of rVE (3.2%).[231, 237, 239] One study[226] conducted their analysis using three different estimates from Coleman et al.,[257] the reported rVE (3.2%), and the 95% confidence intervals (CIs) for the rVE, (-2.5% and 8.4%), citing the non-statistically significant result as their reasoning behind this approach.[226] Another study[229] carried out a rapid review of the data and identified an additional four studies in the year after the publication of Coleman et al..[257] This study obtained a pooled estimate for rVE of 4% (95% CI: -0.05% and 8.4%) for prevention of influenza-related hospitalisations.[229]

rVE of RIIV versus aIIV

Ruiz-Aragón et al.[241] (2023) used a rVE of 10.7% for RIV4 relative to aTIV (in lieu of aQIV) based on an observational study conducted over in those aged 65 years and older.[265] The study was conducted over a single influenza season, and the rVE estimate reported relates specifically to the prevention of influenza-related inpatient stays.[265] This was the sole study identified by the authors as suitable for use,

noting the lack of clinical and observational studies comparing the quadrivalent formulations available.[241]

rVE standard egg-based and cell-based

One of the strategies assessed by Nguyen et al. (2022) compared ccQIV with standard, egg-based QIV in adults aged less than 65 years.[230] Egg-adapted mutations can occur as part of the manufacturing process of the traditional egg-based influenza vaccines, particularly during propagation of the influenza strain A(H3N2).[266] As egg-adaptation does not occur in mammalian cell-based vaccines, they may have higher vaccine efficacy relative to egg-based vaccines, particularly in an 'egg-adapted year' (a year where antigenic mismatch exists between QIV and circulating influenza strains).[266] To account for this potential antigenic mismatch and associated reduced vaccine efficacy of standard QIV (which can occur as a consequence of this), Nguyen et al. reported a rVE of 15.6% for ccQIV for egg-adapted years.[230] This value was estimated from pooled retrospective studies, alongside the rVE of HD-QIV to aTIV when egg-adapted (9%) and when matched (24%). For years which were not reported as egg-adapted, rVE was assumed to be 0%.[230]

Waning rate

None of the studies incorporated a waning rate for immunity, which would be considered an appropriate approach when assessing the cost effectiveness of an annual vaccination programme. Only two of the 19 included studies acknowledged not incorporating a waning rate for immunity. Kohli et al. (2022) assumed one year of full protection after vaccination,[231] while Nguyen et al. (2023) assumed that neither infection nor vaccine-induced protection would wane over one season.[236]

Vaccination coverage

Vaccination coverage was reported in all but one study.[238] An overall coverage rate was reported in six studies,[227-229, 239-241] with rates ranging from 49.5% in Finland[240] to 75% in Denmark.[239] Twelve studies reported age-stratified coverage rates.[223-226, 230-237] In children, these ranged from 1.7% in those aged under four years in Spain,[223] to 27.6% in those aged two to 17 years in Ireland.[236] In working-age adults not at high risk of complications from influenza, coverage rates ranged from 5.2% in those aged 15 to 44 years in Spain,[223] to 47.0% in those aged 55 to 64 years in Canada.[230] Coverage rates modelled in adults aged 65 years and older ranged from 29.3% in Uruguay,[234] to 85.0% in South Korea.[233] In adults aged 75 years and older, rates ranged from 40.0% in Germany,[231] to 80.0% in the UK and Ireland.[225, 226, 236]

Five studies also modelled separate rates for individuals at high risk of complications.[231-234, 236] In children, rates ranged from 3.1%[236] to 9.3%[231] in younger children (aged six months to six years), and 9.2%[231] to 48.6%[236] in older children (aged two to 17 years). Coverage rates in adults of working age ranged from 10.2%[234] to 48.6%.[230] Two of the included studies classified individuals aged 65 years and older as either 'low-risk' or 'high-risk', though notably coverage rates for this age cohort were identical regardless of the level of risk in both studies.[231, 236]

Three studies also modelled a current vaccination coverage rate and target rates for future programmes.[233, 235, 236]

Table 5.4 Vaccination strategies and vaccine characteristics considered in the models evaluating vaccination with an enhanced inactivated influenza vaccine in those aged 65 years and older

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage

Alvarez[240]	2023	1 dose	• HD-QIV
			• Standard QIV
				≥65 years	• VE standard QIV vs strain A: 23.8-50%
					• VE standard QIV vs strain B: 22.7-50%
					• rVE HD-QIV vs standard QIV:
					  • Preventing influenza cases: 24.2%
					  • Preventing influenza-related hospitalization: 17.8% (Belgium, Portugal) and 24.3% (Finland)
						NR	• Belgium: 53.1%
							• Finland: 49.5%
							• Portugal: 59.2%

Bianculli[234]	2022	1 dose	• Standard QIV • Standard TIV	• Children <5 years • Adults ≥65 years • Healthcare professionals • Residents and staff in nursing homes • Pregnant women • High-risk individuals	• VE standard TIV vs strain A across age groups: 51-61% • VE standard TIV vs matched B across age groups: 66-77% • VE standard TIV vs mismatched B across age groups: 44-52% • Cross protection: 67%	NR	• ≤4 years: 23% • ≥65 years: 29.3% *High-risk* • 5-19 years: 10.2% • 20-49 years: 10.2% • 50-64 years: 10.2%

Choi[233]	2022	1 dose	*Programme 1 (baseline):*
			• Standard TIV in ≥65 years
			• Standard TIV or standard QIV (available at out-of-pocket expense) in (i) high-risk adults aged 19-64 years and (ii) adults aged 50-64 years
			
			Programme 2:
				• 19-64 years (HR)
				• 50-64 years
				• ≥65 years
					• VE standard TIV in high-risk populations 19-64 years, and in 50-64 years with no additional risk: 59%
					• VE standard QIV in high-risk populations 19-64 years, and in 50-64 years with no additional risk: 64.2%
					• VE ≥65 years:
					  • Standard TIV: 58%
					  • Standard QIV: 63.2%
					  • aTIV: 66.4%
						NR	*Programme 1 (baseline):*
							• High-risk 19-64 years: 35.8%
							• 50-64 years: 41.4%
							• ≥65 years: 85%
							
							Programme 2 and 3:
							• High-risk 19-64 years: 80%
							• 50-64 years: 80%
							• ≥65 years: 85%

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
			• aQIV in ≥65 years with target vaccination rate of 85% • Standard TIV in (i) high-risk adults aged 19-64 years and (ii) adults aged 50-64 years *Programme 3:* • aTIV in ≥65 years with target vaccination rate of 85% • Standard QIV in (i) high-risk adults aged 19-64 years and adults aged 50-64 years *Programme 4:* • HD-QIV in ≥65 years with target vaccination rate of 85%		• HD-QIV: 72%		
Crepey[223]	2020	1 dose	• Standard QIV • Standard TIV	• ≥65 years • <65 years (HR) (Entire population modelled)	• VE standard QIV vs AH1N1 across age groups: 0-0.67 • VE standard QIV vs AH3N2 across age groups: 0-0.67 • VE standard QIV vs B Victoria across age groups: 0-0.80 • VE standard QIV vs B Yamagata across age groups: 0-0.80 • Cross protection: 70%	NR	• ≤ 4 years: 1.68% • 5-14 years: 1.68% • 15-44 years: 5.22% • 45-64 years: 15.67% • ≥65 years: 58.16%
Fochesato[232]	2022	1 dose	• aQIV • Standard QIV	• Multiple (Entire population modelled)	• VE standard QIV vs AH1N1 across age groups: 62-69% • VE standard QIV vs AH3N2 across age groups: 24-43% • VE standard QIV vs B strain across age groups: 52.1-77% • rVE aQIV vs standard QIV:	NR	• 0-4 years: 4.55% • 5-7 years: 5.18% • 18-49 years: 2.91% • 50-64 years: 15.66% • 65-69 years: 59.84% • 70-74 years: 67.41% • 75-79 years: 68.36% • 80-84 years: 76.39%

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
					• Scenario 1- based on rVE against lab confirmed influenza: 34.6% • Scenario 2 – based on rVE against ILI outcomes for influenza related medical encounters +/- pneumonia in various clinical settings: 13.9%		• ≥85 years: 72.23%
Jacob[239]	2023	1 dose	• aQIV • Standard QIV • HD-QIV	• ≥65 years (further segregated into 65-74 years and ≥75 years)	• VE standard QIV vs AH1N1: 62% • VE standard QIV vs AH3N2: 24% • VE standard QIV vs B strain: 63% • rVE HD-QIV vs standard QIV: 24.2% • rVE aQIV vs HD-QIV: 3.2%	NR	• Denmark: 75% • Norway: 59.7% • Sweden: 60%
Kim De Luca[238]	2023	• 1 dose in adults. • Non-vaccinated children receive 2 doses.	*Strategy 1 (base-case analysis)* • Any vaccine *Scenarios* • Strategy 2: RIV4 age ≥18 years • Strategy 3: HD-QIV age ≥65 years • Strategy 4: aQIV age ≥65 years	Entire population older than 6 months modelled	VE for any vaccine: • 6-23 months: 0.46 • 2-4 years: 0.46 • 5-11 years: 0.44 • 12-17 years: 0.42 • 18-49 years: 0.35 • 50-64 years: 0.40 • ≥65 years: 0.27	NR	• Not specified
Kohli[226]	2021	1 dose	• aQIV • HD-QIV	• ≥65 years (entire population greater than 6 months modelled)	rVE aQIV vs HD-QIV in preventing influenza (3 scenarios modelled, using 3 different rVE estimates): • -2.5% • 3.2% • 8.9%	NR	• 65-74 years: 68% • ≥75 years: 80%

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
Kohli[231]	2022	1 dose	• aQIV • Standard QIV • HD-QIV	• ≥65 years (entire populations older than 6 months modelled)	• VE standard QIV vs AH1N1: 62% • VE standard QIV vs AH3N2: 24% • VE standard QIV vs B strain: 79% • rVE aTIV vs TIVe for reducing medical encounters: 13.9% • rVE of aTIV compared to HD-TIV for reducing medical encounters: 3.2%	Assumed full protection for one year	≥65 years (with or without high-risk): 40%
Marbaix[237]	2023	1 dose	• aQIV • Standard QIV • HD-QIV	• ≥65 years (further segregated into 65-74 years and ≥75 years)	• VE aQIV: 56.1% • VE HD-QIV: 54.7% • VE standard QIV: 40.2%	NA	• 65-74 years: 53.2% •≥75 years: 70.80%
Mattock[225]	2021	1 dose	• HD-TIV • aTIV	• ≥65 years (further segregated into 65-74 years and ≥75 years)	• VE standard TIV vs matched lab-confirmed influenza: 46.0% • VE standard TIV vs mismatched lab-confirmed influenza: 28.0% • VE standard TIV vs hospitalisation: 28.0% • rVE HD-TIV vs standard TIV against lab-confirmed influenza: 24.2% • rVE HD-TIV vs standard TIV against hospitalisation: 24.3% • rVE aTIV vs standard TIV against lab-confirmed influenza: 0% • rVE aTIV vs standard TIV against hospitalisation: 0%	NR	• 65-74 years: 62.7% • ≥75 years: 80%
Nguyen[230]	2022	1 dose	• standard QIV (6 months to 64 years) and aTIV (for ≥65 years)	Entire population modelled from 6 months	• VE standard QIV vs AH1N1 (2012-2019): 9-67% • VE standard QIV vs AH3N2 (2012-2019): 9-66% • VE standard QIV vs B Victoria (2012-2019): 9-72%	NR	• ≥65 years: 75% • 55-64 years: 47% • 6 months to 54 years: 29%

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
			• standard QIV (6 months to 64 years) and HD-QIV (for ≥65 years) • ccQIV (6months to 64 years) and aTIV (≥65 years)		• VE standard QIV vs B Yamagata (2012-2019):9-72% • rVE standard QIV when egg-adapted: 15.6% • rVE HD-QIV vs aTIV when egg adapted: 9% • rVE HD-QIV vs aTIV when matched: 24%		
Nguyen[236]	2023	*Children 2-17 years:* • 1 dose QLAIV *At-risk patients 18-64 years:* •QIV *Adults ≥65 years:* • Standard QIV or • aQIV	• aQIV • Standard QIV • QLAIV	Entire population from 6 months	• VE standard QIV (6 months to 64 years): 54-62.5% • VE standard QIV (≥65 years): 45.3-47% • VE aQIV (≥65 years): 52.9-55% • VE QLAIV (2-17 years): 62.5% • rVE aQIV vs standard QIV: 13.9%	Assumed infection or vaccine-induced protection did not wane during season	• 50-64 years (high risk): 48.6% • 50-64 years (low risk): 40% • 65-74 years (both high and low risk): 68% • ≥75 years (both high and low risk): 80%
Redondo[224]	2021	1 dose	• HD-QIV • aTIV	≥65 years	• VE standard TIV vs strains A and B match (≥65 years): 50% • VE standard TIV vs strain B mismatch ≥65 years): 35% • rVE HD-QIV vs standard TIV against flu: 24.2%	NR	• 65-74 years: 46.9% • ≥75 years: 57.8%

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
					• rVE HD-QIV vs standard TIV against flu hospitalisation: 24.3% • rVE aTIV vs standard TIV against flu cases and against flu hospitalisation: 6%		
Ruiz-Aragón[229]	2022	1 dose	• aQIV • HD-QIV	≥65 years	• rVE HD-QIV vs standard QIV: 24% • rVE aTIV vs HD-TIV: 4%	NR	54.7%
Ruiz-Aragón[241]	2023	1 dose	• RIV4 • aQIV	≥65 years	rVE RIV4 vs aTIV preventing against influenza related inpatient stay: 10.7%	NR	69.4%
Rumi[227]	2021	1 dose	• HD-QIV • Standard QIV	≥65 years	• rVE HD-QIV vs standard QIV: 24.2% *VE in preventing cardiorespiratory hospitalisation:* • Absolute VE standard QIV: 14.6% • rVE HD-QIV vs standard QIV: 18.2%	NR	54.6%
Sandmann[235]	2022	1 dose	Five overall scenarios (with 27 different strategies): • switch those ≥65 years to enhanced TIV i.e. aTIV or HD-TIV • switch those ≥65 years to non-adjuvanted or non-high-dose QIV •adopt mass paediatric (4-16 years) vaccination with standard TIV or standard QIV along with switch to an enhanced TIV for those ≥65 years	• ≥65 years • 4-16 years	• VE TIV vs influenza A: as per ECDC (estimate not provided) • VE standard QIV vs influenza B: standard TIV VE up-scaled using the relative ratio of the 95% confidence interval of the standard TIV to the pooled central	NA	• ≥65 years: 50.9-77.3% (depending on country modelled) • 4-16 years: 10%, 25%, 50% and 75%

Study	Year of Publication	Dosing schedule	Vaccine type	Cohort vaccinated	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
			• adopt mass paediatric (4-16 years) vaccination with standard TIV or standard QIV along with switch to standard QIV for those ≥65 years • combine the vaccination strategies for those ≥65 years and 4-16 years				
Tavares[228]	2022	1 dose	• Standard QIV • Standard TIV	• ≥65 years	• VE standard TIV: 58% • VE standard QIV: 59.9%	NA	50.1%

Key: aQIV – Adjuvanted quadrivalent influenza vaccine; aTIV – Adjuvanted trivalent influenza vaccine; ccQIV – Cell-based quadrivalent influenza vaccine; ECDC – European Centre of Disease Control; HD-QIV – High-dose quadrivalent influenza vaccine; HD-TIV – High-dose trivalent influenza vaccine; HR – High risk; NA – Not applicable; NR – Not reported; OOP – Out-of-pocket payment; QIV – Quadrivalent influenza vaccine; QLAIV – Quadrivalent live-attenuated influenza vaccine; RIV4 – Recombinant quadrivalent influenza vaccine; rVE – Relative vaccine effectiveness; TIV – Trivalent influenza vaccine; VE – Vaccine effectiveness.

5.4.5 Costs (direct and indirect)

Direct costs

The direct costs which were incorporated into the economic models across the 19 studies included the following:

- Direct medical costs:
  - Prescription medication costs including antibiotic and antiviral drug treatment costs
  - GP visits (ambulatory or home visits)
  - ED visits
  - Outpatient and or specialist visits
  - Hospitalisation (including the cost of intensive care treatment, ventilatory support and extra-corporeal membrane oxygenation support)
  - Costs of lifetime care and special education related to long-term sequelae which may occur as a consequence of influenza-related hospitalisation (for example, where debilitating complications such as influenza-related encephalopathy or myositis may occur)[238]
  - Costs related to inpatient and outpatient complications (for example, pneumonia, bronchitis, respiratory disease, heart disease, myocardial infarction (MI), stroke, exacerbation of chronic obstructive pulmonary disease (COPD), central nervous system complications and renal complications)
  - Additional costs incurred where death occurred during an episode of hospitalisation
  - Transport for patients
  - Nursing care costs
  - Other treatment and test costs (for example, X-rays, blood tests, electrocardiography (ECG), audiometry).

- Patient costs:
  - Non-prescription and over-the-counter medication costs
  - Co-payments for drugs and medical treatments
  - Out-of-pocket payments for vaccination in non-target populations.

- Vaccination costs:
  - Vaccine acquisition costs
  - Vaccine administration costs
  - Vaccine-specific medical appointments
  - Costs related to vaccine-related adverse events

- Costs of lifetime care and special education related to long-term sequelae of vaccine-related adverse events (specifically long-term sequelae resulting from Guillain-Barré syndrome).[238]

Indirect costs

The indirect costs incorporated from a societal perspective included costs borne on the individual and their carers. Indirect costs borne on the individual included:

- Productivity losses due to illness, outpatient visits and hospitalisation
- Productivity loss due to premature death
- Loss of earnings
- Time costs for vaccination.

Indirect costs borne by carers included:

- Productivity loss for carers
- Sickness benefit for parental absenteeism.

Six studies reported the methods used to calculate productivity losses, with five studies using the human capital method[229, 231, 233, 234, 241] and one study using the friction cost approach.[232] The data required to measure and value costs are included in the data extraction tables in Appendix A5.2.

5.4.6 Effects (direct and indirect)

Direct effects

Within the reviewed studies, the direct effects of influenza vaccination on the incidence and burden associated with influenza included some or all of the following:

- Incidence of influenza and or incidence of symptomatic influenza cases
- Incidence of non-medically or medically attended cases (where medically attended relates to care provided by a GP, in outpatient departments or through the ED)
- Cases requiring GP visit
- Cases requiring ED visit
- Ambulatory cases with complications
- Hospitalisation for influenza
- Hospitalisation for complications related to influenza
- Influenza-related mortality
- Life-years gained.

Only one study included the effect of vaccine-related adverse events in its model.[238]

Indirect effects

Three studies incorporated indirect effects in their studies. Kohli et al. (2021) included community protection as a scenario analysis,[226] while Sandmann et al. included indirect protection for older people through mass vaccination of children and indirect protection for children by switching older people from a standard TIV to either (i) an enhanced TIV or (ii) standard QIV.[235] Choi et al. also incorporated a community protection effect as part of a scenario analysis, where the relative risk of infection in the adult population was affected by the vaccine coverage rate in children.[233]

Where reported, data required to measure and value effects are included in the data extraction tables in Appendix A5.2.

Utility values for quality-adjusted life years (QALYs)

Baseline utility values used in the analyses were clearly reported for 13 studies.[223-225, 228, 229, 231-234, 237, 239-241] Six studies did not clearly report the baseline utility value used in their QALY calculation.[226, 227, 230, 235, 236, 238] The baseline utility values in three studies considered the presence of individuals at high and low risk of influenza complications in different ways.[231, 233, 234] One study specified that baseline utilities were weighted for chronic conditions in individuals aged under 60 years old,[234] while another weighted baseline utilities for those individuals aged 19 to 64 years who were considered at high risk.[233] One study provided separate baseline utilities for adults aged 65 years and older that were at high and low risk of complications.[231]

Eleven studies clearly provided values for, or reported using, age-group specific baseline utilities in their analyses,[223-226, 231-234, 237, 239, 240] while five studies reported age-group specific QALY losses.[223, 230, 231, 234, 238] One study also presented sex-specific baseline utilities.[240]

Eight studies provided clear explanation of the methods used to derive baseline utility values. Six studies specified using country-specific baseline utility values derived using the Euro-Qol five-dimension (EQ5D) instrument.[225, 228, 229, 235, 240, 241] One study reported using a US-specific time-trade-off survey to derive utility weights,[238] while another study reported using expert opinion to validate foreign utility values for use in a South Korean population.[233]

Across the included studies, utility decrements applied in the case of both influenza and its accompanying health states were poorly reported, with inconsistencies observed in the terms used. Utility decrements reflected the health states included across the studies, and could be grouped as decrements due to influenza-like illness (ILI), influenza, influenza requiring outpatient treatment, influenza requiring inpatient treatment, and decrements due to adverse effects associated with

influenza vaccination. QALY losses due to premature death or quality-adjusted life expectancies were reportedly calculated by nine studies, but estimates for these QALY losses were not provided.[225, 226, 229-231, 234-236, 241] The range of values reported in the studies for both disutilities and QALY losses associated with specific health states can be seen in Table 5.5.

Of the studies which included a health state related to either influenza or ILI that did not require outpatient or inpatient care, six studies reported disutilities applied (values ranging from 0.15-0.32),[225, 227, 229, 237, 240, 241] while a further nine studies reported QALY losses (values ranging from 0.005-0.03).[224, 226, 228, 230-232, 234, 238, 239] In the case of influenza requiring outpatient care, four studies reported disutility values used (ranging from 0.13-0.4),[229, 233, 237, 241] and four studies reported QALY losses for outpatient care without notable complications (ranging from 0.0014-0.009).[223, 235, 236, 239] Two studies also reported QALY losses for outpatient care for specific complications, which included acute otitis media, (community acquired) pneumonia (or CAP), myocardial infarction (MI) and stroke.[231, 239] In the case of influenza requiring inpatient care, disutility values were reported by four studies (ranging from 0.38-0.6),[229, 233, 237, 241] and QALY losses were reported by thirteen studies, which ranged from 0.0034-0.287,[223-226, 228, 231, 232, 235-240] depending on the complication (detailed in Table 5.5). Only one study considered QALY losses related to vaccination-related adverse events or the long-term sequelae of such events.[238]

Table 5.5 Utility values and QALY losses for health states associated with influenza as reported in the economic evaluations examining the cost effectiveness of vaccination with an inactivated influenza vaccine in those aged 65 years and older

Health state	Lowest reported value	Highest reported value	Number of studies	Referenced in
ILI and Influenza				
Disutility				
Influenza	0.247	0.295	2	(225, 240)
Symptomatic influenza	0.15	0.32	4	(227, 229, 237, 241)
QALY loss				
ILI	0.009	N/A	1	(228)
Non-medically attended ILI	0.005	N/A	1	(232)
Medically attended ILI	0.006~	N/A	1	(232)
Influenza	0.0061	0.03	4	(224, 230, 234, 238)
Symptomatic influenza	0.0079	N/A	1	(239)
Uncomplicated influenza	0.0075	0.0088	2	(226, 231)
Influenza (without hospitalisation)	0.009	N/A	1	(228)
Influenza-related symptoms with complications	0.0075	N/A	1	(232)
Influenza requiring outpatient treatment				
Disutility				
Influenza outpatient	0.33	N/A	2	(229, 241)
Influenza uncomplicated outpatient	0.35	N/A	1	(233)
Influenza complicated outpatient	0.4	N/A	1	(233)
Ambulatory care URTI	0.13	N/A	1	(237)
Ambulatory care bronchitis/COPD/pneumonia	0.25	N/A	1	(237)
QALY loss				
Influenza outpatient	0.0014	0.0090	4	(223, 235, 236, 239)
Outpatient care AOM	0.0001	N/A	1	(231)
Outpatient care CAP	0.0063	N/A	2	(231, 239)
Outpatient care MI	0.198	N/A	1	(239)
Outpatient care stroke	0.287	N/A	1	(239)
Influenza requiring inpatient hospitalisation				
Disutility				
Influenza inpatient hospitalisation	0.6	N/A	2	(229, 241)
Influenza uncomplicated hospitalisation	0.4	N/A	1	(233)
Influenza complicated hospitalisation	0.5	N/A	1	(233)
Influenza hospitalisation (attributed to reasons other than MI/stroke)	0.38	N/A	1	(237)
QALY loss				

Influenza inpatient hospitalisation	0.0047	0.03222	12	(223-226, 228, 231, 232, 235, 236, 238-240)
Hospitalisation involving MI	0.1980	0.2102	2	(237, 239)
Hospitalisation involving stroke	0.2554	0.287	2	(237, 239)
Hospitalisation AOM	0.0034	N/A	1	(231)
Hospitalisation CAP/pneumonia	0.0096	0.031	3	(228, 231, 239)
Hospitalisation with heart disease	0.031	N/A	1	(228)
Hospitalisation with respiratory disease	0.031	N/A	1	(228)
Adverse events related to influenza vaccination				
QALY loss				
Systemic reaction	0.00312*	N/A	1	(238)
Anaphylaxis	0.0137*	N/A	1	(238)
Guillain-Barré Syndrome	0.02376*	N/A	1	(238)

Key: AOM – Acute otitis media; CAP – Community-acquired pneumonia; COPD – Chronic obstructive pulmonary disease; ILI – Influenza like illness; MI – Myocardial infarction; N/A – Not applicable; QALY – Quality-adjusted life year; URTI – Upper respiratory tract infection.
* Value reported specifically for adults aged 65+ years.
~ Value reported in study as 0.06, however considering other estimates cited in study, this is believed to be a publication error.

5.4.7 Economic results

All 19 included studies calculated an incremental cost-effectiveness ratio (ICER) reporting the incremental costs per quality-adjusted life year (QALY) gained;[223-241] three studies also reported incremental costs per life year gained.[227, 237, 240] Table 5.6 provides an overview of the economic evaluations examining the cost effectiveness of vaccination with an IIV in those aged 65 years and older. (All figures in Table 5.6 are as reported by the study authors at time of publication, with no adjustments made for inflation, and no currency conversions carried out.)

Studies which considered aQIV as the intervention were all industry funded. The following cost-effectiveness results were reported:

- When compared with standard QIV, the use of aQIV in those aged 65 years and older in Spain was found to be highly cost effective from both a healthcare perspective (ICER of €6,694 per QALY gained) and a societal perspective (ICER of €3,936 per QALY gained) when a rVE of 13.9% was applied; this finding remained when using alternate VE assumptions. It was deemed cost saving when compared with standard QIV from a societal perspective when a rVE of 34.6% was applied.[232]

- A study comparing aQIV with both standard QIV and HD-QIV in Scandinavian countries reported that aQIV was cost effective compared with standard QIV from both a healthcare and societal perspective in each of Denmark (€10,170 per QALY gained from a healthcare perspective; €5,472 per QALY gained from a societal perspective), Norway (€12,515 per QALY gained from a healthcare perspective; €7,906 per QALY gained from a societal perspective) and Sweden (€9,894 gained from a healthcare perspective; €4,856 gained from a societal perspective), while aQIV dominated (that is, was more effective and less costly than) HD-QIV from both perspectives again in all countries.[239] In this study, an rVE value of 24.2% for HD-QIV compared with standard QIV was used, in addition to an rVE of 3.2% for aQIV compared with HD-QIV.[239]

- A study from the UK healthcare perspective found aQIV to be cost saving when compared with HD-QIV, assuming that HD-QIV was priced at the existing list price of HD-TIV.[226] Three different rVE values for aQIV compared with HD-QIV were applied in this study, ranging from -2.5% to 8.9%.[226]

- The cost effectiveness of aQIV compared with standard QIV in a German study depended on the willingness-to-pay threshold employed. ICERs from a societal perspective ranged from €14,500 to €23,000 per QALY gained depending on the number of severe influenza seasons modelled. Additionally, aQIV dominated HD-QIV from a societal perspective modelling 0 to 4 severe flu seasons in 10 seasons. A scenario analysis from a social health insurance perspective followed the same pattern with ICERs up to €26,000 for aQIV versus standard QIV, while aQIV dominated HD-QIV in all scenarios. An rVE value of 13.9% for preventing medical encounters for aTIV compared with standard TIV was applied. The rVE value used for aTIV compared with HD-TIV for the same outcome was 3.2%.[231]

- Marbaix et al. compared aQIV (VE of 56.1%) with standard QIV (VE of 40.2%) and HD-QIV (VE of 54.7%) in those aged 65 years and older in Belgium, Finland and Portugal. The authors reported that, from a healthcare perspective, that the probability of aQIV versus standard QIV being cost effective was 82% at a WTP threshold of €35,000.[237] A scenario analysis comparing aQIV with HD-QIV found aQIV to be cost saving when rVE of aQIV relative to HD-QIV is assumed to be 0%.[237]

- A cost-effectiveness study using Irish data found aQIV (VE of 52.9% to 55%) to be cost effective in those aged 65 years and older, from both a healthcare and societal perspective, compared with standard QIV (VE of 45.3% to 47%).[236]

- In a Spanish CUA, aQIV dominated HD-QIV from both a healthcare and societal perspective when vaccine prices were assumed equal, and rVE values comparing HD-QIV to standard QIV of 24.2%, and rVE of aTIV compared with HD-TIV of 4% were assumed.[229]

Where HD-QIV was considered as the intervention, the following cost-effectiveness results were reported:

- An industry-funded study found that, from a total healthcare payer perspective (including patient co-payments), HD-QIV was cost effective compared with standard QIV in both Belgium (ICER of €1,397 per QALY gained) and Finland (ICER of €9,581 per QALY gained). In Portugal, it was also considered cost effective (ICER of €15,267 per QALY gained) from a healthcare payer perspective (excluding co-payments). An rVE value of 24.2% for HD-QIV compared with standard QIV was assumed throughout the study.[240]

- A Spanish study funded by industry compared HD-QIV with aTIV and concluded it was cost effective at a WTP threshold of €30,000 with a probability of 80% of being cost saving.[224] This study assumed an rVE value of 6% for aTIV compared with standard TIV at preventing hospitalisations, an rVE value of 24.2% for HD-QIV compared with standard TIV for prevention of influenza, and an rVE of 24.3% for HD-QIV compared with standard TIV for prevention of hospitalisation.[224]

- Another Spanish study, which was also industry-funded, reported that HD-QIV dominated standard QIV with a probability of 100% at a WTP level of €15,000.[227] This study applied an rVE value of 24.2% for HD-QIV compared with standard QIV.[227]

- A study funded by the South Korean government reported that HD-QIV (VE of 72%) was cost saving from a societal perspective compared with standard TIV (VE of 58%) in adults aged 65 years and older when modelled with 85% coverage.[233] However, productivity losses were not considered for the patients themselves in this age cohort as they were assumed to be retired.[233]

One Spanish industry-funded study which compared the recombinant QIV (RIV4) vaccine with aQIV (using a rVE of 10.7%) reported an ICER of over €100,000 per QALY gained from a societal perspective. Scenario analysis deemed that, in order to meet a Spanish WTP threshold of €25,000, RIV4 would need to have a rVE greater than 34% compared with aQIV.[241]

Another industry-funded study compared the cost effectiveness of HD-TIV with aTIV in England and Wales from a healthcare perspective and reported an ICER of £1,932 per QALY gained for adults aged 65 years and older; this was considered to be cost effective.[225] When further disaggregated into age groups, HD-TIV dominated aTIV in adults aged 75 years and older. However, this assumed a rVE for aTIV of 0% versus standard TIV, in the base-case analysis, alongside an rVE for HD-TIV of 24.2% (for prevention of laboratory-confirmed influenza) and 24.3% (for prevention of hospitalisation) compared with standard TIV. The authors conducted two scenario analyses which considered higher rVE estimates for aTIV versus standard TIV. They found that while remaining cost effective in both adults aged 65 years and older and those aged 75 years and older, the ICER for HD-TIV versus aTIV rose above the assumed WTP threshold of £20,000.[225]

The cost-effectiveness results of the three studies which investigated standard QIV as the intervention compared with standard TIV are summarised below:

- An industry-funded study conducted for Uruguay found standard QIV to be cost effective compared with standard TIV (where VE of standard QIV assumed to be equivalent to the VE of a matched standard TIV) from both a healthcare and societal perspective overall, but ICERs in individual age groups exceeded a WTP threshold of US$20,000 in all age groups under 65 years of age.[234]
- Another industry-funded study reported that standard QIV was cost effective when compared with standard TIV from both a healthcare perspective (ICER of €2,751 per QALY gained) and a societal perspective (ICER of €1,527 per QALY gained) in adults aged 65 years and over in Spain.[223]
- A study funded by the Portuguese government reported that standard QIV (VE of 59.9%) was not cost effective when compared with standard TIV (VE of 58%) from a healthcare perspective with an ICER of €26,403,007 per QALY gained, which was higher than any possible ceiling ratio established by the National Health Service.[228]

Three studies compared a variety of vaccination scenarios. The following cost-effectiveness results were reported:

- A study funded by the South Korean government compared a variety of vaccination scenarios (see Table 5.6).[233] The authors reported that, from a societal perspective, in those aged 65 years and older, HD-QIV was cost saving compared with standard TIV, aTIV was cost effective compared with standard TIV, and standard QIV was not cost effective when compared with standard TIV at a WTP threshold below per capita GDP of Korea.[233] This

study also assessed the cost effectiveness of expanding the national influenza immunisation programme to cover various categories of adults aged 19 to 64 years, who at present may avail of standard TIV and standard QIV at their own expense. From a societal perspective, standard TIV was found to be cost saving and standard QIV was cost effective in adults aged 50 to 64 years when compared with the current regime (where standard TIV or standard QIV are available to this age cohort out-of-pocket). The authors also assessed this intervention from a healthcare perspective only and found that neither standard TIV nor standard QIV were cost effective. In an alternate scenario, where the national influenza immunisation programme was expanded to all 'at risk' adults aged 19 to 64 years, standard TIV and standard QIV were both found to be cost saving from a societal perspective when compared with the current regime (where standard TIV or standard QIV are available at the patients' own expense). From a healthcare perspective, while standard TIV was found to be cost effective in 'at-risk' adults aged 19 to 64 years, standard QIV was not found to be cost effective in this cohort.[233]

- In an industry-funded Canadian study, changing standard QIV to aTIV in those aged 65 years and older, and continuing the use of standard QIV in those aged under 65 years, was found to be cost saving from a healthcare perspective; changing to HD-QIV for those aged 65 years and older was found not to be cost effective based on a WTP threshold of CAD $50,000.[230] A further comparison considering aTIV in those aged 65 years and older in addition to either (i) a cell-based QIV (ccQIV) or (ii) standard QIV in those aged under 65 years found that the combination of aTIV in those aged 65 years and older and standard QIV in those aged under 65 years was found to be more cost effective.[230]

- A large-scale EU-funded modelling study compared 27 different vaccination strategies across five scenarios (see Table 5.6) in eight EU regions and reported that, using an ICER of €15,000 per QALY gained, a mass paediatric vaccination programme using standard QIV was the most cost-effective option.[235] Combining a paediatric programme with either aTIV or HD-TIV in those aged 65 years and older resulted in the highest mean net benefits with ICERs of less than €35,000 per QALY gained at a 50% or 75% mass paediatric vaccine uptake. It also reported that due to community effects, with increased paediatric vaccination coverage there was a decreasing likelihood that vaccination of adults aged 65 years and older would be cost effective.[235]

One government-funded US study compared vaccination against influenza with any vaccine versus no vaccination, from both a societal and a healthcare perspective,

producing ICERs for various age cohorts and risk status (See Table 5.6).[238] When considered from a societal perspective, ICERs for vaccinating non-high-risk individuals aged between six months and 64 years varied between $32,000 per QALY gained (in those aged two to four years) to $194,000 per QALY gained (in those aged 18 to 49 years). Vaccination was found to be cost saving from a societal perspective in high-risk adults aged 50 years and older, while for high-risk children, the ICERs reported varied from $1,500 per QALY gained (in those aged two to four years) to $40,000 per QALY gained (in those aged 12 to 17 years). When considered from a healthcare perspective, this trend continued, but vaccination was considered more cost effective. In non-high-risk individuals, ICERs varied from $13,000 per QALY gained (in those aged two to four years) to $131,000 per QALY gained (in those aged 18 to 49 years). Vaccination was cost saving compared with no vaccination in high-risk individuals between six months and four years of age and in individuals aged 50 years and older. In those aged 12 to 17 years, an ICER of $8,000 per QALY gained was reported.

Three studies also reported ICERs per life year (LY) gained. Alvarez et al. reported ICERs below €10,000 per LY gained in Belgium, Finland and Portugal for HD-QIV versus standard QIV.[240] Rumi et al. found that HD-QIV dominated standard QIV in cost per LY gained.[227] Marbaix et al. reported an ICER of €15,967 per LY gained in favour of aQIV versus standard QIV for Belgian adults aged 65 years and older.[237]

Jacob et al. reported net monetary benefits (NMB) alongside their ICERs, showing that aQIV compared with standard QIV provided NMBs ranging from approximately €5 million to €12.9 million from a healthcare perspective, and approximately €6.3 million to €16.1 million from a societal perspective.[239] Comparing aQIV with HD-QIV provided NMBs of approximately €5.5 million to €10 million from a healthcare perspective, and €5.6 million to €10.25 million from a societal perspective.[239] A positive incremental NMB indicates cost effectiveness at the WTP threshold.[267]

Table 5.6 Results of the economic evaluations examining the cost effectiveness of vaccination with an inactivated influenza vaccine in those aged 65 years and older

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
aQIV									
Fochesato[232]	2022	Spain	aQIV	Standard QIV	≥65 years	• €2,240/QALY at rVE 34.6% • €6,694/QALY at rVE 13.9%	• aQIV cost saving at rVE 34.6% • €3,936/QALY at rVE 13.9%	€25,000/QALY	aQIV cost effective over standard QIV.
Jacob[239]	2023	• Denmark • Norway • Sweden	aQIV	Standard QIV	≥65 years	• Denmark: €10,170/QALY • Norway: €12,515/QALY • Sweden: €9,894/QALY	• Denmark: €5,472/QALY • Norway: €7,906/QALY • Sweden: €4,856/QALY	€30,000/QALY	• aQIV cost effective over standard QIV. • aQIV dominant over HD-QIV.
Kohli[231]	2022	Germany	aQIV	Standard QIV	≥65 years	• €17,200/QALY (4 severe seasons) • €20,000/QALY gained (2 severe seasons) • €26,000/QALY (0 severe seasons)	• €14,500/QALY (4 severe seasons) • €17,200/QALY gained (2 severe seasons) • €23,000/QALY (0 severe seasons)	No established threshold value in Germany	• aQIV cost effective over standard QIV depending on the threshold value. • aQIV also dominant over HD-QIV in all scenarios.
Marbaix[237]	2023	Belgium	aQIV	Standard QIV	≥65 years	€15,227/QALY	N/A	€35,000/QALY	• aQIV cost effective over standard QIV. • aQIV dominant over HD-QIV.
Nguyen[236]	2023	Ireland	aQIV	Standard QIV	≥65 years	€12,970/QALY	€2,420/QALY	€45,000/QALY	aQIV cost effective over standard QIV.
Kohli[226]	2021	UK	aQIV	HD-QIV	≥65 years	aQIV dominant over HD-QIV	aQIV dominant over HD-QIV	£20,000/QALY	aQIV dominant over HD-QIV (assuming that HD-QIV is priced at the existing list price of HD-TIV).

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
Ruiz-Aragón[229]	2022	Spain	aQIV	HD-QIV	≥65 years	aQIV dominant over HD-QIV	aQIV dominant over HD-QIV	€25,000/QALY	aQIV dominant over HD-QIV.
HD-QIV									
Alvares[240]	2023	• Belgium • Finland • Portugal	HD-QIV	Standard QIV	≥65 years	• Belgium: €1,397/QALY • Finland: €9,581/QALY • Portugal: €15,267/QALY	N/A	• Belgium: €35,000/QALY • Finland: €23,000/QALY • Portugal: €25,000/QALY	HQ-QIV cost effective over standard QIV.
Rumi[227]	2021	Italy	HD-QIV	Standard QIV	≥65 years	HD-QIV dominates standard QIV for base-case hospitalisations for influenza and cardiorespiratory events (cheaper and more effective) in both € per QALY and LY	N/A	€30,000/QALY	HD-QIV dominant over standard QIV, with a probability of being 100% cost effective at a WTP level of €15,000/QALY.
Redondo[224]	2021	Spain	HD-QIV	aTIV	≥65 years	€24,353/QALY	N/A	€25,000/QALY	HD-QIV is at least as cost effective as aTIV in individuals aged ≥65 years and may become the dominant strategy when all the consequences of influenza (e.g. cardiorespiratory events) are considered in the assessment.
HD-TIV									

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
Mattock[225]	2021	• England • Wales	HD-TIV	aTIV	• ≥65 years • 65-74 years • ≥75 years	• ≥65 years: £1,932/QALY • 65-74 years: £14,175/QALY • Dominant in ≥75 years	N/A	£20,000/QALY	HD-TIV is as cost effective as aTIV in populations aged ≥65 years.
RIV4									
Ruiz-Aragón[241]	2023	Spain	RIV4	aQIV	≥65 years	N/A	€101,612/QALY	€25,000/QALY	RIV4 is not currently cost effective over aQIV based on current vaccine price and efficacy estimates.
Standard QIV									
Bianculli[234]	2022	Uruguay	Standard QIV	Standard TIV	• Overall cohort • ≤4 years • 5–19 years (HR) • 20–49 years (HR) • 50–64 years (HR) • ≥65 years	• $18,368/QALY • $23,461/QALY • $24,320/QALY • $97,256/QALY • $56,368/QALY • $12,291/QALY	• $18,224/QALY • $23,434/QALY • $24,181/QALY • $94,909/QALY • $55,238/QALY • $12,259/QALY	$20,000/QALY	Standard QIV cost effective over standard TIV for overall cohort and for individuals ≥65 years old.
Crepey[223]	2020	Spain	Standard QIV	Standard TIV	• <65 years HR • ≥65 years	€2,751/QALY	€1,527/QALY	€25,000/QALY	Standard QIV is an efficient intervention over standard TIV.
Tavares[228]	2022	Portugal	Standard QIV	Standard TIV	• ≥65 years	€26,403,007/QALY	N/A	No established threshold value in Portugal	Standard QIV is not cost effective at WTP thresholds of €30,000/QALY or €34,000/QALY.
Numerous strategies									

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
Choi[233]	2022	South Korea	Various (see strategy)	• ≥65 years: Standard TIV • (i) At-risk adults aged 19-64 years and (ii) adults aged 50-64 years: Standard TIV or QIV (available to both groups at out-of-pocket expense)	• Program 2: - Standard QIV in ≥65 years (target vaccination rate of 85%) - Standard TIV in (i) at-risk adults aged 19-64 years and (ii) adults aged 50-64 years (target vaccination rate of 80%) • Program 3: -aTIV in ≥65 years (target vaccination rate of 85%) - Standard QIV in (i) at-risk adults aged 19-64 years and (ii) adults aged 50-64 years (target vaccination rate of 80%) • Program 4: HD-QIV in ≥65 years with target 85%	*19–64 years (at-risk):* • Standard TIV $23,020/QALY • Standard QIV $53,050/QALY *50–64 years:* • Standard TIV $37,352/QALY • Standard QIV $86,463/QALY	*19-64 years (at-risk):* • Both standard TIV and QIV cost saving *50-64 years:* • Standard TIV cost saving • Standard QIV $3,661/QALY *≥65 years:* • Standard QIV $46,486/QALY • aTIV $34,314/QALY • HD-QIV cost saving	One GDP per capita	• Both standard TIV and QIV are expected to be cost effective in those aged 50-64 years. • Enhanced QIV's favoured over standard vaccines in those ≥65 years.

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
Nguyen[230]	2022	Canada	Various (see strategy)	Standard QIV	• Strategy 1: Standard QIV (6 months-64 years) +aTIV (for 65+) • Strategy 2: Standard QIV (6 months-64 years) + high-dose QIV (HD-QIV for 65+) • Strategy 3: ccQIV (6months -64 years) + aTIV (65+)	• Strategy 1: Cost saving • Strategy 2: CAD €81,300/QALY • Strategy 3: CAD €1,300/QALY	N/A	CAD 50,000	• Strategy 1 (aTIV for ≥65 years) was the most cost effective strategy. • Strategy 2 (HD-QIV for ≥65 years) was not cost effective, owing to the high cost per dose of vaccine though improvements were observed in case numbers, hospitalisations and deaths compared with the baseline scenario.

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
Sandmann[235]	2022	• England • France • Ireland • The Netherlands • Portugal • Scotland • Spain • Navarre (Spain)	Various (see strategy)		Five overall scenarios (with 27 different strategies): • switch those aged ≥65 years to an enhanced TIV i.e. aTIV or HD-TIV • switch those aged ≥65 years to non-adjuvanted non-high-dose QIV • adopt mass paediatric (4-16 years) vaccination with standard TIV or QIV along with switch to an enhanced TIV for those aged ≥65 years • adopt mass paediatric (4-16 years) vaccination with standard TIV or QIV along with switch to standard QIV for ≥65 years • combine the vaccination strategies for those aged ≥65 years and 4-16 year olds.	• A mass paediatric vaccination programme, with or without move of those aged ≥65 years to an enhanced TIV, has the highest probability of being cost effective at €15,000/QALY. • Moving those aged ≥65 years to an enhanced TIV plus adopting mass paediatric standard QIV programmes provides the highest mean net benefits in all settings at €25,000/QALY gained (with 10% mass paediatric uptake), €30,000/QALY gained (25% mass paediatric uptake), and €35,000/QALY gained (50% or 75% mass paediatric uptake).	N/A	N/A	Results support a combination of switching population aged ≥65 years to an enhanced TIV and adopting universal paediatric vaccination programmes across the European settings.

Study	Year Published	Country	Intervention	Comparator	Strategy	ICER - Healthcare Perspective	ICER - Societal Perspective	WTP threshold	Study Conclusions
Any vaccination									
Kim De Luca[238]	2023	US	Any vaccination	Unvaccinated	*Non-high-risk:* • 6-23 month • 2-4 years • 5-11 years • 12-17 years • 18-49 years • 50-64 years *High risk:* • 6-23 month • 2-4 years • 5-11 years • 12-17 years • 18-49 years • 50-64 years • ≥65 years	 • $20,000/QALY • $13,000/QALY • $27,000/QALY • $41,000/QALY • $131,000/QALY • $50,000/QALY • Cost saving • Cost saving • $5,000/QALY • $8,000/QALY • $4,000/QALY • Cost saving • Cost saving	 • $45,000/QALY • $32,000/QALY • $63,000/QALY • $95,000/QALY • $194,000/QALY • $80,000/QALY • $12,000/QALY • $1,500/QALY • $29,000/QALY • $40,000/QALY • $23,000/QALY • Cost saving • Cost saving	NR	Routine annual influenza vaccination remains attractive for most age and risk groups from an economic perspective.

Key: aQIV – Adjuvanted quadrivalent influenza vaccine; aTIV – Adjuvanted trivalent influenza vaccine; CAD – Canadian dollar; ccQIV – Cell-based quadrivalent influenza vaccine; GDP – Gross domestic product; HD-QIV – High-dose quadrivalent influenza vaccine; HD-TIV – High-dose trivalent influenza vaccine; HR – High risk; ICER – Incremental cost-effectiveness ratio; LY – Life years; N/A – Not applicable; NR – Not reported; OOP – Out-of-pocket payment; QALY – Quality-adjusted life year; QIV – Quadrivalent influenza vaccine; RIV4 – Recombinant quadrivalent influenza vaccine; rVE – Relative vaccine effectiveness; TIV – Trivalent influenza vaccine; VE – Vaccine effectiveness; WTP – Willingness to pay.

5.4.8 Reported study conclusions

Of the seven studies assessing vaccination with aQIV, all deemed it to be cost effective from the chosen perspective. The analysis from Spain concluded that, from both healthcare payer and societal perspectives, aQIV vaccination was highly cost effective in those aged 65 years and older compared with standard QIV.[232] A second Spanish study concluded that mass vaccination effort with aQIV, which was identified to be a less expensive vaccine with comparable effectiveness to HD-QIV, could result in cost savings from both a direct medical payer and societal perspective.[229] The study from Scandinavian countries concluded that aQIV vaccination may be cost effective compared with standard QIV and cost saving compared with HD-QIV in Denmark, Norway and Sweden from both healthcare payer and societal perspectives.[239] The study from Germany reported that vaccinating with aQIV may be cost effective compared with standard QIV depending on the WTP for additional health benefits, from both healthcare payer and societal perspectives. The authors also reported that, since the VE values for aQIV and HD-QIV are similar, aQIV was cost saving when compared with HD-QIV at the current prices.[231] The study from the Belgian healthcare payer perspective came to the same conclusion while also noting that an influenza season of increased severity would further improve the cost effectiveness.[237] The study from Ireland concluded that vaccination with aQIV was cost effective in those aged 65 years and older when compared with standard QIV from both a healthcare payer and societal perspective, while noting it could also result in a modest reduction in excess bed occupancy when the impact of co-circulating COVID-19 was considered.[236] The study from the UK concluded that given current effectiveness evidence and list prices, aQIV was cost saving compared to HD-QIV.[226]

Of the studies solely assessing HD-QIV as the intervention, all three found it to be cost effective versus the comparator in the chosen perspective. An Italian study concluded that vaccination with HD-QIV in those aged 65 years and older was cost effective compared with standard QIV.[227] It was also found to be cost effective in Belgium, Finland and Portugal from differing healthcare sector perspectives, reporting that vaccinating with HD-QIV compared with standard QIV would result in a lower incidence of influenza, lower healthcare resource usage and lower premature mortality, while being cost effective.[240] The study comparing HD-QIV vaccination with aTIV vaccination in those aged 65 years and older living in Spain, found HD-QIV to be at least as cost effective as aTIV and could be cost saving when the broader consequences of influenza were considered in the analysis.[224] A study comparing HD-TIV vaccination with aTIV from a healthcare payer perspective in England and Wales reported that HD-TIV was cost effective at the WTP threshold of £20,000 per QALY gained in those aged 65 years and older.[225]

Five studies directly compared aIIVs with HD-IIVs, all of which were industry funded, with some inconsistencies seen in the results. In each of these five studies, the authors found the sponsor's vaccine to be either more cost effective than the comparator (aIIV compared with HD-IIV),[226, 229, 230] or at least as cost effective (HD-IIV compared with aIIV) as the comparator.[224, 225]

A study compared RIV4 with aQIV in those aged 65 years and older living in Spain. From a societal perspective, it was not cost effective based on vaccine prices and rVE assumptions.[241]

Three studies compared standard QIV with standard TIV and reported conflicting cost-effectiveness results. The study from Spain reported that replacing standard TIV vaccination with standard QIV would be cost effective from both a National Health Service (NHS) and societal perspective, with maximum benefits observed in those aged 65 years and older.[223] The study from the perspective of the Portuguese NHS payer perspective reported that switching to standard QIV was not cost effective at either of the two WTP threshold values considered (that is, €30,000 per QALY gained and €34,000 per QALY gained) in the absence of an established threshold value for Portugal.[228] The study from Uruguay reported that switching from standard TIV to standard QIV vaccination would be cost effective overall in all eligible populations.[234]

Of the studies which compared multiple vaccination scenarios, Sandmann et al. concluded that across European settings, modelled results supported the vaccination of those aged 65 years and older with either aTIV or HD-TIV along with the introduction of a universal paediatric vaccination programme from the healthcare payer perspective.[235] In South Korea, Choi et al. concluded that the introduction of either standard TIV or standard QIV for those aged 50 to 64 years and for those aged 19 to 64 years at increased risk of complications from influenza ('at-risk' group) would be cost effective from both healthcare payer and societal perspectives. The authors also reported that the use of highly immunogenic vaccines (HD-QIV or aTIV) in those aged 65 years and older are likely to be favoured over standard TIV or standard QIV from a societal perspective.[233] A Canadian study by Nguyen et al. (2022) concluded that using a ccQIV to vaccinate those aged less than 65 years, combined with aTIV in those aged 65 years and older was cost effective from a healthcare perspective, and resulted in the greatest decrease in incidence of influenza, hospitalisations and mortality.[230] The authors also found that a second vaccine strategy, using HD-QIV in adults aged 65 years and older in combination with a standard QIV in those aged six months to 64 years, also led to a decreased incidence of influenza, hospitalisation and mortality, but noted that the higher cost of HD-QIV was the driving factor in the poor cost-effectiveness results for this intervention.

The sole study to compare vaccination with any vaccine (including standard IIVs, LAIVs, HD-QIVs, RIV4s and ccQIVs) against no vaccination concluded that vaccination was cost effective for most subgroups (from both a healthcare payer and societal perspective) except in working-age adults who were not considered to be at high risk of complications.[238]

5.4.9 Critical appraisal

A critical appraisal of all included studies was undertaken using the framework for quality assessment of decision-analytic models as proposed by Philips et al.[221] Although the overall appraisal of the quality of included studies did not raise major concerns, there were some issues identified within each of the three quality domains assessed. In terms of the 'Structure' domain, 10 of the included studies lacked clarity on the identity of the primary decision-maker,[223, 224, 226, 227, 229, 230, 232, 235, 239, 241] while two studies did not explicitly specify the study perspective adopted.[230, 241] There was concern over two studies which discussed all available vaccines, but did not justify the exclusion of feasible options,[230, 241] while another study excluded a combination of vaccines in the comparison, which hindered a full analysis of the options.[229] A variety of static and dynamic models were used, usually citing WHO recommendations[268] as the justification for use of a static model.[268] However, four studies used static models where a dynamic model may have been more appropriate[233, 234, 239, 240] due to the inclusion of epidemiological influential subgroups such as children, and also for consideration of community immunity (also known as herd immunity), as stated in the WHO recommendations.[268] Some studies reported the time horizon adopted as a 'single influenza season' but did not clearly specify whether this encompassed a six-month or twelve-month time period, though either time period would be considered appropriate.[225, 234]

In the 'Data' domain, overall there was a scarcity of reporting on the methods of data identification and quality appraisal without justification. In four studies, there was some concern in regard to the choice of the data sources used and assumptions made based on these choices.[224, 230, 238, 241] Concerns were identified in regard to the level of detail provided for some parameter data, including rVE and assumptions used to extrapolate results, the use of utility weights and reporting of QALY losses. A number of studies were not sufficiently clear on details of the data that were incorporated into the model.[225, 226, 229, 230, 233, 236, 240, 241] Less than half of the studies appraised were comprehensive in their assessment of uncertainty, with methodological and structural uncertainty the most often neglected.[226, 231-233, 235, 237-239]

Finally, within the 'Consistency' domain, a quarter of the studies did not provide any description of internal consistency or model validation.[224, 225, 227, 228, 238] The majority

of models were sufficient in their consideration of external consistency, but two studies did not cite their results in comparison to other findings.[227, 230]

5.5 Discussion

5.5.1 General and model characteristics

This rapid review provides information on the methodologies used by economic modelling studies (published from 1 January 2020 up to 23 July 2023) in high-income countries. It examines modelling of vaccination with an IIV in adults aged 65 years and older as well as studies that included a subgroup consisting of those aged 65 years and older. Of the 19 studies included in this review, 15 studies were conducted for EU/EEA countries and four in non-EU/EEA countries. Five studies were multi-centre studies and 14 studies adopted a single country perspective. Fifteen of the 19 studies were industry-funded.

Type of Model

Static decision-tree models were most commonly used (n=10 studies), followed by decision tree with dynamic transmission models (n=7 studies). In a number of cases (n=4 studies), static models were incorrectly used where a dynamic model would have been considered a more appropriate choice, specifically where vaccination strategies modelled included an epidemiologically influential subgroup within the modelled population.[268] An epidemiologically influential subgroup could be defined as a distinct subgroup within the modelled population for whom prevention of transmission is particularly desirable, either because they are considered at increased risk of severe disease from infection, and or due to their potential for increasing transmission of the virus (for example, children, individuals with clinical conditions that puts them at increased risk of disease and, when considered as part of an entire population model, adults aged 65 years and older). In comparison with the 2022 systematic review by Loong et al.,[219] it is clear that dynamic transmission models are becoming more commonly used to model vaccination strategies against seasonal influenza, though static decision-tree models remain the most common modelling strategy employed.

When modelling infectious diseases, dynamic transmission models can be favoured, as they facilitate modelling of community immunity and can capture the indirect effect of reducing influenza transmission across an entire population. Notably, a Spanish study which adopted both a static and dynamic approach when modelling the efficiency of seasonal influenza vaccination found that vaccination was only efficient using a dynamic model, which they attributed to the indirect community protection inferred on the unvaccinated population.[269] However, community immunity would be influenced by vaccine coverage rates, the rate of change of

circulating influenza viruses in the community and how vaccine efficacy fares against this rate of change. Modelling community immunity for influenza may be limited by the potential uncertainty associated with these parameters, particularly given the adaptive nature of the disease and short time horizon typically adopted in the models.

Dynamic models must include an entire population cohort. While the objective of this HTA is to estimate the clinical and cost effectiveness of universal vaccination with an enhanced IIV in those aged 65 years and older, it may be appropriate to consider the impact of a change in vaccination strategy in this age cohort within the context of the overall national influenza vaccination strategy. In Ireland, annual influenza vaccination is reimbursed by the Health Service Executive (HSE) for individuals aged 65 years and older; for children aged two to 17 years of age; for other groups who are either at higher risk of complications due to influenza or who reside with or care for these individuals; and for some occupational groups including healthcare workers.[44] Consequently, if conducting an economic evaluation using a dynamic model, it may also be appropriate to model other influenza vaccination strategies targeting influential groups to give a true estimation of any community effects which may develop. In this instance, the use of parameter estimates specific to each age-cohort and subgroup within the population would be preferable and consequently the validity of any model results will be limited by the availability and accuracy of such estimates. This would need to be considered when deciding whether to use a dynamic transmission model as part of this HTA.

Use of a static model will not account for positive externalities associated with community immunity and so may underestimate the value of vaccination by only considering direct protection of the vaccinated individual.[270] However, it is considered an acceptable approach by the WHO and in particular for influenza vaccination where there is no epidemiologically influential subgroup.[268] Current Irish national guidelines advise that individuals aged 65 years and older should be considered eligible for influenza vaccination and do not identify any epidemiologically influential subgroups within this age cohort.[11] Thus using a static decision-tree model could be considered an appropriate and conservative approach for an economic evaluation if the population being modelled is restricted to adults aged 65 years and older.

Time horizon

The majority of the included studies modelled cost effectiveness over a time horizon of one year or less. This is appropriate given both the adaptive nature of influenza, where variation exists in the dominant strains circulating annually, and consequently the limited duration of immunity that vaccination may infer. A disadvantage of this

approach is that shorter time horizons may not capture the true burden of any serious health complications of either influenza or vaccine-related adverse events, nor any potential ongoing costs which may be associated with these complications, which can be more common and more severe in older people. However, the validity of any results from a cost-effectiveness analysis conducted over a longer time horizon would be limited by the uncertainty associated with vaccine effectiveness estimates. Taking an approach of a shorter time horizon may provide a more conservative and more reasonable estimate of cost effectiveness.

Perspective

Seven included studies conducted their analysis from a dual perspective in the base-case scenario. Two studies did not clearly specify the perspective adopted for the analysis.[230, 241] Without knowledge of the perspective taken, the appropriateness of the methodological approach adopted is difficult to evaluate, as the perspective taken will inform any costs and effects included in the model. Perspective is considered a minimum reporting requirement in health economic evaluations, and international HTA agencies specify in their own guidelines as to which perspective should be adopted in the reference case.[271, 272]

Typically economic evaluations conducted as part of HTA in Ireland are conducted from the perspective of the payer, or healthcare sector.[273] However, adopting this perspective would limit evaluation of a vaccination programme to direct medical costs and effects and would then neglect to capture indirect economic benefits, such as productivity losses avoided that would have resulted from illness or premature death.[270] The WHO recommends that, when conducting economic evaluations of an infectious disease, a societal perspective should be adopted for the base-case analysis unless this contradicts national guidelines.[268] There is scope within HIQA's guidelines to conduct an economic evaluation from an alternative perspective if considered appropriate.[273] It has previously been established in the protocol for this HTA that a societal perspective will be adopted.

Health states

Overall, the health states included in the models adequately reflected the nature of the disease of influenza and considered potential for treatment associated with both outpatient and inpatient care. The included studies differed in their approaches as to how inpatient care was defined. In some cases, models considered inpatient care and or hospitalisations as a single state, whereas others classified inpatient care into further subcategories according to specific complications. Accounting for hospitalisations as a single health state in the model may not adequately capture the significant costs and effects associated with the secondary complications which could occur following influenza infection, which could lead to undervaluation of the cost

effectiveness of any interventions. However, given the dearth of parameter data for these secondary complications, the simplified inpatient health state could be considered a more appropriate choice and may produce a more conservative estimate of cost effectiveness.

Discount rates

An intervention such as seasonal influenza vaccination will incur an immediate cost and health effect, but some costs and effects may continue to be experienced many years after the intervention takes place. While direct costs, such as those relating to vaccine administration, will be incurred within the time horizon of the modelled studies, other costs and effects, such as those associated with long-term complications of influenza and quality adjusted life-years gained, will be experienced into the future. Applying a discount rate to any costs or effects occurring after one year reflects a societal preference for valuing present costs and effects higher than future costs and effects.[274] Discount rates can vary by jurisdiction, and are typically set out by national health technology assessment agencies.[275]

Throughout the included studies, a range of discount rates were applied. Discount rates were not typically applied to direct costs, which would be considered an appropriate approach given that direct costs relating to influenza are likely to be accrued over the shorter time horizons of one influenza season, or one year. In one US study, which modelled an entire population cohort, a discount rate was applied to costs associated with permanent outcomes occurring in those aged under 18 years of age as a result of influenza or vaccine-related adverse events.[238]

Discount rates were typically applied to indirect effects associated with the societal perspective, such as productivity losses and QALY losses due to premature death. A minority of included studies clearly specified that QALYs were discounted over a lifetime horizon. This would be an appropriate approach where a model accounted for disutilities associated with serious complications of influenza, such as a myocardial infarction (MI) or stroke, where utility decrements would be anticipated beyond a shorter time horizon. Three studies conducted an analysis over multiple seasons and specified that QALY losses were discounted, but did not clearly outline the time horizon over which health outcomes were followed.[226, 230, 231]

5.5.2 Intervention and vaccination strategies

Heterogeneity was observed across the studies included in this review in terms of the type of interventions modelled. The primary differences in methodological approach among the included studies pertained to both the population modelled and the population which were targeted by various vaccination strategies. Nine of the 19 included studies modelled populations limited to adults aged 65 years and older, and

considered vaccination strategies that were applied to this entire cohort. An additional eight studies included entire populations in their models, and modelled vaccination strategies targeting multiple cohorts, while two studies included entire populations in their models, but only modelled vaccination strategies in adults aged 65 years and older. When developing the de novo economic model for this HTA, there is a need to consider whether the modelled population should be limited to those aged 65 years and older, or should include multiple cohorts.

As identified in Chapter 3, the burden associated with influenza is highest in older age groups. This said, the omission of younger age cohorts from any model may result in undervaluing the total burden associated with influenza, particularly in relation to societal costs such as productivity losses associated with informal care-giving and work-related absences. Omission of children and younger adults at high risk of complications from a modelled population would overlook the effect of existing vaccination strategies on community immunity in a dynamic transmission model. However, a static model would facilitate an approach where only individuals aged 65 years and older, the target population for this HTA, are considered.

The most frequently modelled vaccination strategy was the use of an aQIV compared with either a standard QIV or HD-QIV. The cost effectiveness of a HD-QIV as an intervention was also analysed against an aTIV and standard QIV and standard TIV. Only one study compared a RIV4 as an intervention against an aQIV, which may be attributed to the lack of evidence regarding the relative vaccine efficacy of RIV4.[241]

Fifteen of the 19 included studies were industry funded, which likely influenced the choices of strategies assessed. Of these 15 studies, 11 studies assessed the cost effectiveness of the study sponsor's vaccine compared to a rival's vaccine,[224-226, 229-232, 236, 237, 239, 241] while four studies compared the manufacturers enhanced vaccine to their own standard IIV.[223, 227, 234, 240] Of the four remaining studies, which received government or research funding, two studies assessed strategies targeting multiple cohorts, where enhanced vaccines were considered in those aged 65 years and older,[233, 235] one study compared a standard QIV with a standard TIV,[228] and one US study assessed cost-effectiveness of vaccination (with any vaccine) across multiple cohorts compared with no vaccination.[238]

Details of dosing schedules were omitted from all but one study,[238] however it is reasonable to assume that these omissions may infer that one vaccine dose was administered per influenza season, consistent with the typical licensed indications for these vaccines.

5.5.3 Vaccine characteristics

The composition of the seasonal influenza vaccine changes annually based on WHO recommendations, and the vaccine efficacy for each influenza season then depends on whether the most dominant circulating strains have been correctly anticipated. As such, there are inherent difficulties when estimating vaccine efficacy.

Three differing approaches to estimating VE were adopted across the included studies. The estimates used related to either VE versus influenza, VE versus specific viral strains of influenza, or rVE, with estimates obtained from a range of sources including RCTs, meta-analyses and observational studies. There was little agreement in terms of the values for VE used, which may be attributed to both the range of interventions analysed across studies and the range of sources used, though the majority of studies provided justification for the choice of estimates. There was greater consistency observed in the sources of rVE values used, which is likely due to the lack of high-quality studies conducted in this area. The WHO Guide on Standardization of Economic Evaluations of Immunization Programmes advises that estimates for VE should be taken from RCTs and meta-analyses where possible, owing to a potential risk of bias associated with individual observational studies.[268] In some cases, age-stratified estimates were used; this may be considered an appropriate approach given that immunosenescence (that is, the deterioration of the immune system associated with advancing age) would be expected in the older age cohort under consideration for this economic evaluation.

The variability in approaches is primarily a result of the lack of available VE estimates for enhanced QIVs, owing to their relatively recent market availability. In the case of both enhanced and standard QIVs, many of the VE and rVE estimates used in the included studies were extrapolated from corresponding TIV estimates due to the limited evidence available for the quadrivalent formulations. This is a pragmatic approach to take given the absence of available evidence and the similarities in composition between the trivalent and quadrivalent vaccines. The quadrivalent vaccine must be assumed to be at least as effective as its trivalent equivalent, and more so depending on how well the quadrivalent vaccine matches the B strains circulating in an influenza season.

Waning rate for immunity was not accounted for in any of the included studies in this review, which is considered appropriate where a short time horizon is adopted for an analysis.

Assumed vaccine coverage rates varied greatly across the included studies and within the individual age cohorts. Coverage rates for those aged 75 years and older ranged from 40% to 85% and, for those aged 65 years and older, they ranged from 30% to 80%. Variability is expected, given that coverage rates adopted should be

country-specific. However, coverage rates can also vary within a country year-on-year. In addition, trends in vaccine uptake may also be difficult to predict and could to be influenced by multiple factors. For example, in Ireland, seasonal influenza vaccination coverage rates among adults aged 65 years and older have been higher in the period post COVID-19 than pre-COVID-19. Notably, a small decline in coverage was reported in the most recent influenza season (2022-2023) relative to the previous year, although it is worth remembering that data for the most recent season are at present incomplete.[276] It is possible that increased immunisation demands on a population could result in vaccine fatigue, which may potentially result in a lower vaccine uptake and consequently lower coverage rates in subsequent years.[277] Conversely, it is possible that coverage rates could be seen to increase following a severe influenza season, or a season where COVID-19 or RSV was particularly virulent and or transmissible. To account for this unpredictability, it is imperative that the most recent seasonal influenza vaccination coverage rates in Ireland be used as input parameters in the economic evaluation conducted as part of this HTA and varied within an appropriate range as part of the sensitivity analyses conducted.

5.5.4 Costs and effects

Costs

The direct medical costs associated with influenza were largely consistent across studies and reflected the health states of the models. GP visits and hospitalisations were the most frequently reported direct costs, though some studies also considered a separate ED cost in addition to inpatient care. Direct medical costs pertaining to vaccination acquisition were consistently included. A minority of studies also included direct costs associated with vaccine administration. However, in the economic evaluation being undertaken as part of this HTA, parameters for vaccine administration would be expected to be the same in both intervention and comparator arms of the analysis, thus their inclusion may not be necessary. It may be relevant to include costs associated with vaccine wastage as part of an economic model, given the price differential that likely exists between enhanced IIVs compared with standard IIVs.

One study which modelled multiple cohorts included costs of lifetime care and special education related to long-term sequelae which may occur as a consequence of either an influenza-related hospitalisation or a vaccine-related adverse event (specifically Guillain-Barré syndrome).[238] The study only provided two examples of events which would be considered a consequence of influenza-related hospitalisation (influenza-related encephalopathy or myositis) and did not comprehensively outline the specific complications included in this costing, which makes it difficult to evaluate

the appropriateness of its inclusion in the model. These direct costs were included for individuals aged under 18 years only. While not clearly specified in the analysis, it could be inferred that the cost of special education is directly related to education of the patient over their lifetime, rather than education of healthcare providers at the point of care.

Two studies included costs related to mortality for specific complications. One Spanish model included a medical cost to be applied in the event of death.[223] A Portuguese study provided an estimate for an episode of hospitalisation, and a second estimate appeared to incorporate the cost of hospitalisation and additional mortality costs jointly.[228] Neither study provided clarity as to what these medical costs associated with death pertained to. While a post-mortem charge may be expected, some of the figures quoted are quite significant. Consequently, it is difficult to evaluate their suitability for inclusion in the model.

Where a societal perspective was adopted, indirect costs were typically evaluated using a human capital approach, accounting for productivity losses due to both illness and premature death. Productivity losses could be anticipated as higher in a dynamic transmission model, where an entire population would be included and productivity losses associated with informal care-giving and work-related absences would then be considered. In contrast, if a static model is chosen, modelling a population of 65 years and older, it would be anticipated that productivity losses would not be as significant, as the majority of the modelled population are expected to have left the workforce. This is an important consideration when contemplating model choice, as a static model may limit an appropriate analysis from a societal perspective.

Direct costs to the patient, including transport, nursing and out-of-pocket payments, were considered in the minority of studies. In Ireland, all individuals aged over 70 years are eligible for a GP visit card and are consequently eligible for free medical visits, but may still be required to pay out of pocket for prescription medications and hospital charges.[278] Given that the age cohort being assessed as part of this HTA is adults aged 65 years and older, it would be considered appropriate to include relevant out-of-pocket payments as part of a societal perspective, regardless of whether a static or dynamic model is chosen.

Effects

Health outcomes were measured in QALYs in the majority of the included studies, while life years gained and life years lost were also listed as outcome measures in two studies each. Across studies, utility decrements were poorly reported, with inconsistencies observed in the terminology used. Studies reported a range of disutilities and QALY losses associated with various health states, capturing the

effect of ILI, influenza, GP visits and hospitalisation on quality of life. In the case of hospitalisations, disutilities associated with specific complications of disease were used in a minority of instances.

Disutilities used in the analyses also varied in terms of whether disutility was applied per event or whether the value quoted represented disutility per day spent in a health state. Across studies, the duration associated with influenza only was reported within a narrow range of five to seven days, whereas mean length of inpatient stay showed more variation, with one multi-jurisdiction study quoting a duration within a range of six to 20 days for each jurisdiction.[240] In the economic evaluation conducted as part of this HTA, efforts should be made to ensure that the absolute disutility for inpatient stay reflects the typical length of stay based on applicable Irish data.

Only one study considered vaccine-related adverse events as an outcome in their analysis. Enhanced influenza vaccines are associated with a higher risk of local adverse events at the injection site, thus their inclusion as a direct outcome as part of any economic evaluation could be justified.[279]

5.5.5 Reported study conclusions

Across the included studies, both aQIV and HD-QIV were concluded to be a consistently more cost-effective strategy for individuals aged 65 years and older, from both a healthcare and societal perspective (when compared with a standard QIV), with ICERs falling within WTP thresholds for the respective countries. When vaccination with aQIV was compared with HD-QIV, aQIV was the more cost-effective strategy, which could be attributed to the lower modelled acquisition cost of aQIV relative to HD-QIV. One study comparing RIV4 to aQIV reported an ICER far above an acceptable WTP threshold value, and concluded that RIV4 was not cost effective compared with aQIV considering both current vaccine cost, and limited rVE evidence available.[241]

Notably, 15 of the 19 included studies were industry-funded. Previous research has shown that sponsorship bias is prevalent in health economic evaluations,[280] across multiple disease areas,[281-283] thus the possibility of bias should be considered when discussing the results obtained. In each of these 15 industry-funded studies, the authors found either (i) in favour of the study sponsor's own vaccine,[226, 229-232, 236, 237, 239, 241] or (ii) in favour of their enhanced vaccine where compared with their own standard quadrivalent or trivalent product,[223, 227, 234, 240] or (iii) found their product to be at least as cost effective as a rivals.[224, 225] The potential for bias is evident given that the results of five industry sponsored studies which directly compared aIIVs with HD-IIVs did not find consistently in favour of one vaccine, but rather results aligned with the industry sponsor's vaccine in each instance.

Of the four remaining studies, which received government or research funding, two studies also found in favour of enhanced vaccines over standard vaccines in those aged 65 years and older,[233, 235] one study found vaccination with standard QIV was not cost effective when compared with standard TIV,[228] and one US study found vaccination (with any vaccine) across multiple cohorts to be cost effective when compared with no vaccination.[238] Though there are limited independently conducted studies which examine enhanced IIVs, the results were in agreement with those which were industry-funded. Furthermore, the critical appraisal of all included studies found that methods of data identification were not always well reported, with particular concerns and around the level of detail and sources provided for some parameters, including VE and rVE estimates and utility values. This further increases the risk of bias in the economic results, though notably these concerns could be found across all studies, and were not limited to those which were industry-funded.

The included studies frequently highlighted that the true burden of influenza was likely underestimated, owing to difficulties obtaining a laboratory-confirmed influenza diagnosis and the possibility that hospitalisations and deaths may be attributed to secondary comorbidities which could potentially occur as a consequence of influenza. ICER values were reported as robust to variation in parameter values in the sensitivity analyses performed across the included studies.

5.5.6 Conclusion

The objective of the rapid review was to examine the approaches taken to modelling the expected costs and benefits of vaccination with an IIV in those aged 65 years and older in high-income countries. The findings of this review will inform the development of a de novo economic model to assess the cost effectiveness of universal vaccination with an enhanced IIV in those aged 65 years and older in Ireland. Seven of 19 economic evaluations included in this review adopted a dual perspective when assessing the cost effectiveness of an intervention. The primary differences in methodological approach were related to the type of model chosen and whether multiple cohorts were modelled, or whether the modelled population was restricted to individuals aged 65 years and older. Static decision-tree models were the most common model choice across the included studies, though these were often not an appropriate choice given the population being modelled. Dynamic transmission models were also commonly used and can be advantageous when modelling infectious diseases owing to their ability to capture indirect community effects.

Heterogeneity was also observed in the parameter estimates chosen for vaccine efficacy, though some of this variation could be attributed to the breadth of vaccination strategies examined across studies. There was little agreement across

studies in the values for VE used, though greater consistency was observed in the sources and values of rVE used. Included health states were largely consistent across models and conformed to the nature of the disease, though some models incorporated a larger number of health outcomes, specifically considering serious secondary complications associated with influenza, the inclusion of which would increase the potential to capture the true burden of the disease. The included studies consistently found both aQIV and HD-QIV to be cost effective compared with standard quadrivalent and trivalent alternatives, with ICERs falling within WTP threshold values in the case of adults aged 65 years and older. Notably, all 15 of the industry-funded studies found the manufacturers' preferred vaccine to be cost effective, which highlights the potential for sponsorship bias across studies, and must be considered when appraising the economic results. The findings of this review will be considered when developing the de novo economic model of universal vaccination with an enhanced IIV in those aged 65 years and older in Ireland.

6 Economic evaluation

Key points

- A dynamic transmission model was developed that describes the transmission and incidence of notified cases of influenza in the general population in Ireland in an average influenza season. It incorporates both the current HSE Seasonal Influenza Vaccination Programme and the impact of switching from a standard inactivated influenza vaccine (IIV) to an enhanced IIV for those aged 65 years and older.
- Given evidence of a statistically significant improvement in one or more clinical outcomes relative to standard IIV in a population aged 65 years and older, the model specifically assessed the following two enhanced IIVs:
    - high-dose inactivated influenza vaccine (HD-IIV)
    - adjuvanted inactivated influenza vaccine (aIIV).
- From the payer perspective, of the three strategies considered, and assuming that the standard IIV is procured at the list price of €10.99, it was estimated that:
    - A strategy based on aIIV dominated the existing strategy based on standard IIV, being less costly and more effective (more quality-adjusted life years (QALYs)) and would therefore be considered cost saving.
    - A strategy based on HD-IIV was both more costly and more effective than an aIIV-based strategy. The incremental cost-effectiveness ratio (ICER) for this comparison was estimated at €76,731 per QALY gained and therefore would be considered not cost effective at a willingness-to-pay (WTP) threshold of €45,000 per QALY.
    - At a WTP threshold of:
        - €20,000 per QALY, aIIV had the highest probability of being the cost-effective strategy (65.2%), followed by standard IIV (27.6%).
        - €45,000 per QALY, aIIV again had the highest probability of being the cost-effective strategy (55.4%), followed by HD-IIV (22.9%).

- The sensitivity analysis highlighted that the estimates of cost effectiveness were highly sensitive to a number of parameters, including the relative costs of the enhanced IIVs (compared with standard IIV). Given the high degree of uncertainty, a number of scenario analyses were conducted where the relative costs of the vaccines were varied, both alone and in combination, to understand the impact on the ICERs. At a WTP threshold of €20,000 per QALY, the results indicated that:
    - where the difference in unit cost between aIIV and standard IIV was €8 or less, a strategy with aIIV had the largest net monetary benefit
    - where the difference in unit cost between aIIV and standard IIV was €9 or more, a strategy with standard IIV had the largest net monetary benefit
    - where the difference in unit cost between aIIV and standard IIV was between €8 and €9, there remains a high degree of uncertainty as to whether a strategy with standard IIV or aIIV would generate the largest net monetary benefit
    - HD-IIV generated the largest net monetary benefit only where the difference in cost between it and aIIV was €9 or less and the cost of standard IIV was between €5 and €10.99.
- Assuming that the standard IIV is procured at the list price of €10.99, it was estimated that the one-year incremental budget impact of strategies based on aIIV and HD-IIV (versus standard IIV) was -€316,000 (95% CI: -5.1 million to 3.6 million) and €11.3 million (95% CI: 0.7 to 22.1 million), respectively.
    - Increased expenditure on procurement of the aIIV (€3.8 million) was offset by savings in the cost of hospitalisation (€4.1 million) due to the higher clinical effectiveness of aIIV (compared with standard IIV) in reducing influenza-related hospitalisation in those aged 65 years and older.
    - Increased spending on procurement of HD-IIV (€18.9 million) was partially offset by cost savings (€7.6 million) from reductions in hospitalisations, GP visits and prescription medications for those with GP visit or medical cards, due to the higher clinical effectiveness of HD-IIV, compared with standard IIV, in preventing influenza.

- The budget impact estimates were also subject to a high degree of uncertainty, and the scenario analysis highlighted that the results are highly sensitive to changes in the relative cost of the vaccines.
- The modelling study is subject to a number of limitations. As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values. Specifically, it is noted that the evidence base to support improved clinical effectiveness with the aIIV and HD-IIV is limited, with the estimates for both vaccine types based on single studies. Sensitivity and scenario analyses demonstrated that the findings are largely robust with the exception of the uncertainty over vaccine prices.
- The results demonstrated that the outcome of this economic evaluation is highly sensitive to the assumed relative unit costs of a dose of aIIV and HD-IIV (compared with standard IIV) and that this should be a key consideration in any decision-making and in procurement negotiations with vaccine manufacturers.

6.1 Introduction

This chapter describes the development of an epidemiological model of influenza infection for Ireland and the associated economic evaluation. The evaluation, comprising cost-utility and budget impact analyses, was used to estimate the costs and benefits associated with switching from a standard (IIV) to an enhanced IIV for those aged 65 years and older in Ireland as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme.

6.2 Development of the Epidemiological Model

6.2.1 Objective

An epidemiological model of influenza was developed to characterise the incidence of influenza disease in Ireland in the context of the current HSE Seasonal Influenza Vaccination Programme which offers a standard inactivated influenza vaccine (standard IIV) to eligible adults aged 18 years and older and a live attenuated vaccine (LAIV) to eligible individuals aged 2 to 17 years. The model was then used to assess the impact on incidence of influenza in the population of switching to an enhanced IIV for those aged 65 years and older. Health state outputs obtained from the epidemiological model were used in the economic evaluation of an enhanced IIV for those aged 65 years and older.

6.2.2 Model overview

As a communicable disease, modelling for economic evaluation of influenza must take into consideration its transmissible nature. The influenza virus has a non-constant force of infection which is dependent on the number of infectious individuals in the population, contact patterns between individuals, and the probability of infection given contact with an infectious person. In contrast to non-communicable diseases, an intervention such as vaccination also typically produces population-level effects, such as community immunity, in addition to benefits for those who are directly reached by a vaccination programme. Given this, a dynamic transmission model was deemed to be the most appropriate in order to model the full range of effects across the population associated with switching to an enhanced IIV for those 65 years and older.

A probabilistic, age-structured dynamic transmission model of influenza was developed for Ireland. The model structure was informed by a review of economic models published for high-income countries (Chapter 5). The model, developed in R® (version 4.1.2), describes the transmission and incidence of notified influenza in the general population in Ireland, incorporating both the current HSE Seasonal Influenza Vaccination Programme and the impact of switching to an enhanced IIV for those aged 65 years and older. As the model represents notified cases, it excludes suspected cases of influenza that were not laboratory confirmed and influenza-like illness (ILI).

To establish the base-case scenario, the epidemiological model was calibrated to an average influenza season in Ireland using observed notified influenza case data from five past influenza seasons (from 2017/2018 to 2023/2024, excluding 2020/2021 due to the impact of COVID-19). The model was built using Irish demographic data and epidemiological data of notified influenza cases sourced from the Health Protection Surveillance Centre (HPSC).[284] In the absence of relevant published Irish data, age-specific contact data from the UK subset of the POLYMOD were used to characterise the spread of the influenza virus.[285]

6.2.3 Population

A population of approximately five million people was stratified into six age cohorts, based on the current population distribution in Ireland,[286] as follows:

- 0 to 17 years
- 18 to 49 years
- 50 to 64 years

- 65 to 69 years
- 70 to 74 years
- 75 years and older.

6.2.4 Model structure

The epidemiological model is a mathematical representation, using a system of differential equations of influenza virus transmission and the occurrence of influenza disease with both the current vaccination strategy for the entire population and a strategy incorporating an enhanced IIV for those aged 65 years and older. A simplified model structure is presented in Figure 6.1, illustrating a number of distinct epidemiological states (mutually exclusive compartments) and the movement of individuals (arrows) through the states. The model also incorporates a seasonality function to capture the seasonal peak of influenza cases.

6.2.5 Model flows

This model represents notified influenza cases only. Individuals follow a pathway of either natural influenza progression or, following vaccination, either protection from influenza or susceptibility to influenza. Natural influenza progression comprises four influenza disease states (susceptible, latent, infectious and recovered). The vaccination pathway comprises three influenza vaccination states where individuals are either fully protected (one-dose protected), vaccinated but susceptible or, where there is vaccine failure, susceptible. Although not presented in Figure 6.1, mortality, both all-cause and influenza-related, is continuous in the model. A detailed description of the model flows is provided below and the differential equations for each age group are provided in Appendix A6.1.

Natural influenza disease pathway

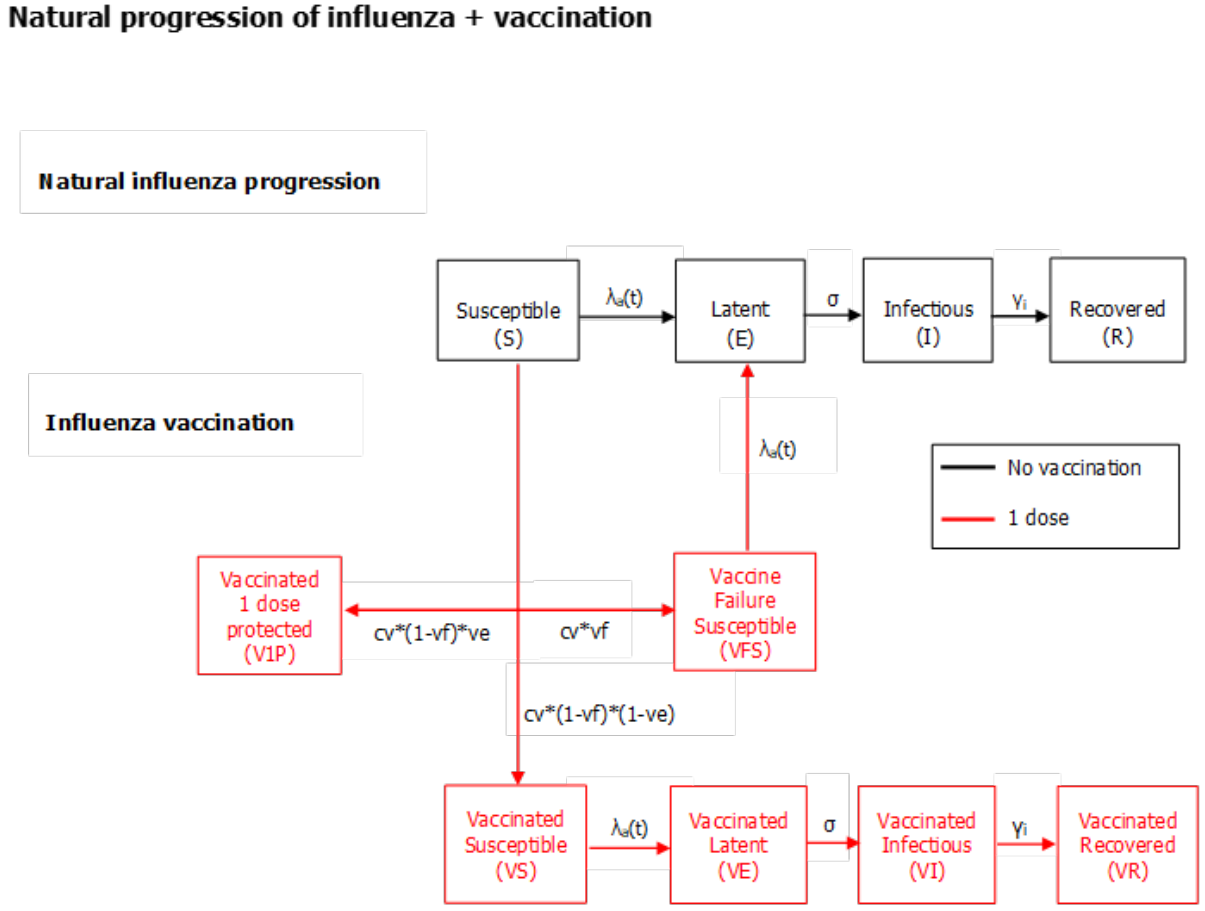
By their nature, epidemiological models are a simplification or approximation of real processes. These simplifications may reflect the absence of reliable data to develop and parameterise more sophisticated models, and that greater complexity does not necessarily result in more accurate outputs. A parsimonious model was therefore developed to support decision-making. For this model, it was assumed that all individuals are susceptible (S) at the start of the influenza season. Susceptible individuals who become infected with influenza move to the latent state (E) at a rate given by the age-dependent force of infection, λ_a. The rate of movement from E to the infectious state (I) is given by the duration of the latent period for influenza, σ. The rate of movement from I to the recovered state (R) is given by the duration of the infectious period for influenza, γ_i. It was assumed that individuals only get influenza once in a season.

Influenza vaccination pathway

The model examined vaccination of those aged 65 years and older with either a standard IIV or an enhanced IIV using the following simplified vaccination pathway. Following one dose of a vaccine:

- a proportion of individuals remain susceptible to influenza due to vaccine failure, *vf*. These individuals move from S to the vaccine failure susceptible state (FVS) and become infected with influenza at the same age-dependent force of infection rate as susceptible individuals who are not vaccinated, λ_a
- among those who seroconvert (that is, develop immunity) after one dose, a proportion of individuals (*1-vf)*, corresponding to the first dose vaccine effectiveness, *ve*, is protected and moves from S to the vaccinated 1-dose protected state (V1P). The model assumes no waning of immunity over the course of a single season for those who are initially protected. The remaining proportion, *1-ve*, remains susceptible and moves from S to the vaccinated susceptible state (VS). It was assumed that those in the VS state can be infected with breakthrough influenza and move to the vaccinated latent state (VE) at an age-dependent force of infection rate, λ_a. The rate of movement of individuals from VE to the vaccinated infectious state (VI) is given by the duration of the latent period, σ. The rate of movement of individuals from VI to the vaccinated recovered state (VR) is given by the duration of the infectious period with breakthrough influenza, γ_i.

Figure 6.1 Model structure



Key: cv – coverage; vf – vaccine failure; ve – vaccine effectiveness; $\lambda_a(t)$ – force of influenza infection by age group; σ – duration of latency period; γ_i – duration of infectious period for influenza.

6.2.6 Initial model states

All individuals were assumed to start the influenza season in the susceptible compartment, with the exception of two individuals from each age group, where one individual was in each of the latent and infectious compartments. These seed cases were required to initialise the model and enable the subsequent spread of infection in the model.

6.2.7 Contact matrix

The risk that the influenza virus causes influenza, or the force of infection, is a function of the number of infected people in the population, the average number of contacts per unit of time, and the probability of infection given contact. Daily contact data from the UK subset of the POLYMOD dataset were used to characterise the spread of influenza virus to cause influenza.[285] The UK matrix, which includes

home, work, school, leisure, transport and other contact rates, was adjusted to align with the age groups specified in our epidemiological model. The contact matrix is provided in Appendix A6.2

6.2.8 Model input parameters

Biological and vaccine-related model input parameters are provided in Table 6.1 and Table 6.2, respectively. These parameter estimates were informed by Chapters 3, 4 and 5 and are described in greater detail in Section 6.3. The enhanced vaccines that were considered were limited to those for which a statistically significant vaccine effect had been demonstrated in those aged 65 years and older.

6.2.9 Model output

The model was run in one-day intervals for six months over a single influenza season. The model output provided the number of individuals in each age group for each of the disease states, for all vaccines under consideration, for each day over the time period.

6.2.10 Assessment and quantification of uncertainty

To enable an assessment of uncertainty, probabilistic sensitivity analysis (PSA) was conducted to test the impact of parameter uncertainty and the robustness of the epidemiological model outputs.

Sensitivity analysis

Parameter uncertainty was assessed using a Monte Carlo simulation with 1,000 iterations. A number of epidemiological parameters (vaccine effectiveness of standard influenza vaccine for three separate age groups and the relative vaccine effectiveness of high-dose inactivated influenza vaccine (versus standard inactivated influenza vaccine) in preventing influenza in those aged 65 years and over) were defined by a statistical distribution to represent uncertainty in the mean parameter value. For each parameter, an appropriate statistical distribution was selected. Parameter values were then drawn as random variates from their specified distributions and the total number of notified influenza cases was recalculated. From the 1,000 simulations, in 770 instances the total number of notified influenza cases was within the range of observed incidence from five past influenza seasons (from 2017/2018 to 2023/2024, excluding 2020/2021) (Appendix A6.3). A subset of 250 simulations were randomly selected for inclusion in the PSA for the economic model. As a statistically significant reduction in laboratory-confirmed influenza was not demonstrated for adjuvanted inactivated influenza vaccine, the same vaccine effectiveness as standard inactivated influenza vaccine was assumed in the

epidemiological model. However, a statistically significant reduction in hospitalisations associated with laboratory-confirmed influenza was demonstrated for adjuvanted inactivated influenza vaccine (Chapter 4); this was incorporated into the economic model (see Section 6.3).

Model validation and calibration

External and internal validation of the epidemiological model was conducted in accordance with HIQA's Quality Assurance Framework. All model inputs, calculations, and model outputs were reviewed by a second economic modeller.

Table 6.1 Biological input parameters

Parameter	Parameter name	Parameter description	Parameter values	Source
μ_{ac}	All-cause mortality rate	Annual all-cause mortality rate (by age group)	0-17yrs: 0.0235% 18-49yrs: 0.0793% 50-64yrs: 0.4359% 65-69yrs: 1.1253% 70-74yrs: 1.9255% ≥75yrs: 7.0096%	Central Statistics Office[287]
μ_{infl}	Influenza-related mortality rate	Annual influenza-related mortality rate (by age group)	0-17yrs: 0.0000% 18-49yrs: 0.0002% 50-64yrs: 0.0036% 65-69yrs: 0.0123% 70-74yrs: 0.0133% ≥75yrs: 0.0741%	Health Protection Surveillance Centre (as outlined in Chapter 3; section 3.4.3)
$\lambda_a(t)$	Force of influenza infection	Force of influenza infection (by age group), where: $\lambda_a(t) = z(t) * \sum_{a'} \beta_a((I_{a'} + VI_{a'})/N)$ [1] $z(t) = 1 + \delta \sin\left(\frac{2\pi(t-t_0)}{365}\right)$ [2] $\beta_a = c_{a,a'} * \rho_a$ [3] z(t) = sinusoidal seasonality function[288] β = influenza infection rate by age group I = number of infectious people by age group VI = number of infectious people in those vaccinated (breakthrough) N = total number of people	Ongoing calculation for each age group	Calculation within model
		δ = amplitude of the seasonality function z(t) defined in [2]. δ determines the peak value of the basic reproduction number ($0 \leq \delta \leq 1$)	0.40	Model calibration

Parameter	Parameter name	Parameter description	Parameter values	Source
		t_0 = reference time for the seasonality function z(t) defined in [2]	-0.04766	Model calibration
		$c_{\alpha,\alpha'}$ = average number of contacts that a susceptible person in age group α makes per day with a person in age group α'.	Appendix A6.2	Contact matrix[285]
		ρ_α = the probability of a susceptible person in age group α becoming infected with influenza given contact with an infectious person	0-17yrs = 0.04016 18-49yrs = 0.02736 50-64yrs = 0.03931 65-69yrs = 0.06932 70-74yrs = 0.09484 ≥75yrs = 0.26694	Calibration
σ	Latency rate for influenza	Average duration of latent infection = 1/σ	1 day	Chapter 5
γ_i	Recovery rate from influenza	Average duration of influenza infection = $1/\gamma_i$	2 days	Chapter 5

Table 6.2 Vaccination input parameters

Parameter	Parameter name	Parameter description	Base-case parameter values	Source
CV	Coverage rate	Vaccination coverage rate (by age)	<18 years: 15% 18-49yrs: 11% 50-64yrs: 30% 65-69yrs: 62% 70-74yrs: 76% ≥75yrs: 87%	Assumed based on uptake of LAIV (2-17 years) and standard IIV (≥18 years) for existing influenza immunisation programme[115]
VF	Vaccine failure	Probability of complete vaccine failure	5%	[289]
VE	Vaccine effectiveness	Effectiveness of standard influenza vaccine by age	<18 years: 57.7% (95% CI: 35.7 to 72.1) 18-64yrs: 51.6% (95% CI: 45.1 to 57.3) ≥65yrs: 34.0% (95% CI: 23.7 to 43.0)	Meta-analysis based on data from I-MOVE and VEBIS studies. See section 4.2.1 for details.
rVE HD-IIV*	Relative VE of HD-IIV in preventing influenza	Relative VE of HD-IIV in preventing influenza (versus standard IIV)	24.2% (95% CI: 9.7 to 36.5)	Chapter 4
rVE aIIV†	Relative VE of aIIV in preventing hospitalisation	Relative VE of aIIV in preventing hospitalisation for influenza (versus standard IIV)	59.2% (95% CI: 14.6 to 80.5)	Chapter 4

Key: CI – confidence interval; CV – coverage rate; HD-IIV – high-dose inactivated influenza vaccine; I-MOVE – Influenza - Monitoring Vaccine Effectiveness; IIV – inactivated influenza vaccine; rVE – relative vaccine effectiveness; VE – vaccine effectiveness; VEBIS – Vaccine Effectiveness, Burden and Impact Studies; VF – vaccine failure.

*rVE estimate was limited to HD-IIV as this is the only enhanced IIV for which a statistically significant reduction in laboratory-confirmed influenza in those aged 65 years and older was found (Chapter 4).

†rVE estimate was applied to aIIV based on the results from Chapter 4. As reported in Chapter 4, HD-IIV was not associated with a statistically significant reduction in influenza-related hospitalisations relative to standard IIV. Based on the evidence of increased clinical effectiveness against laboratory-confirmed influenza for HD-IIV relative to standard IIV, a pro-rata reduction (24.2%) in hospitalisations was allowed in the model.

6.3 Economic Evaluation

6.3.1 Methods

The economic evaluation was conducted in line with national HTA guidelines,[273] reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement,[290] and undertaken in R Studio[291] and Microsoft Excel 2013.[292]

Study objective

The purpose of the health economic evaluation was to estimate the cost effectiveness and budget impact of offering vaccination with an enhanced IIV instead of a standard IIV to those aged 65 years and older in Ireland. The cost-utility analysis (CUA) estimates the incremental costs and outcomes of alternative vaccination strategies with an enhanced IIV, while the budget impact analysis (BIA) provides a means of predicting the potential financial impact of switching to an enhanced IIV.

Target population

The target population for vaccination with an enhanced IIV was adults aged 65 years and older, but the model also captures the indirect benefits for the entire population. For the model, the target population for the intervention comprised an annual cohort of approximately 806,000 adults aged 65 years and older (based on 2023 CSO population estimates).

Technology

The technology being assessed was one-dose, enhanced IIV administered as part of the HSE Seasonal Influenza Vaccination Programme. This includes vaccination of eligible individuals in primary care settings such as GP practices, community pharmacies and in residential care facilities. The aim of the technology is to reduce influenza infection and thereby reduce influenza-related disease. A detailed description of the technology is provided in Chapter 2.

As outlined in Chapter 4, evidence of increased clinical effectiveness relative to standard IIVs specific to the population aged 65 years and older was found for two of the four enhanced vaccine types considered in this HTA:

- laboratory-confirmed influenza cases with high-dose inactivated influenza vaccines (HD-IIVs)
- hospitalisations associated with laboratory-confirmed influenza with adjuvanted inactivated influenza vaccines (aIIVs).

As such, the economic evaluation was limited to an assessment of a potential switch to one of these two enhanced vaccine types.

6.3.2 Comparator

The following three alternative vaccination strategies were assessed in this economic evaluation:

- current HSE Seasonal Influenza Vaccination Programme with standard IIV administered to those aged 65 years and older
- current HSE Seasonal Influenza Vaccination Programme with aIIV administered to those aged 65 years and older
- current HSE Seasonal Influenza Vaccination Programme with HD-IIV administered to those aged 65 years and older.

6.3.3 Study design

A CUA was undertaken to estimate the incremental cost and health benefits associated with using an enhanced IIV in the HSE Seasonal Influenza Vaccination Programme. Health benefits were expressed in terms of quality-adjusted life years (QALYs) gained, which reflect the impact of the intervention on patients' quality and quantity of life. The CUA was undertaken using the outputs from the epidemiological model previously described and simulated the costs and patient outcomes associated with notified cases of influenza.

The BIA estimated the incremental cost to the HSE of offering an enhanced IIV instead of a standard IIV in the HSE Seasonal Influenza Vaccination Programme to those aged 65 years and older.

6.3.4 Economic model structure

The dynamic transmission model described above estimated the incidence of notified cases of influenza in a hypothetical population cohort, divided into six age groups, with standard influenza vaccines administered to those aged less than 65 years (LAIVs for those aged 2 to 17 years and standard IIVs for those aged 18 to 65 years)) and either a standard or an enhanced IIV (aIIV and HD-IIV) administered to those aged 65 years and older. The disease state outputs relating to incidence of disease were subsequently used in the economic model that was developed in MS Excel.

For all influenza vaccines under consideration, it was assumed that those infected with influenza (specifically, notified cases) could develop severe disease requiring hospitalisation. Additionally, it was assumed that those vaccinated against influenza

could develop breakthrough influenza, possibly leading to hospitalisation. Costs and QALYs were assigned to each of the health outcomes for all influenza vaccination strategies, enabling the calculation of the incremental costs and incremental QALYs associated with vaccination with an aIIV or a HD-IIV instead of a standard IIV.

Similarly, for the influenza vaccination strategies considered in this assessment, the BIA model also assumed that those infected with influenza could develop severe disease requiring hospitalisation and all those vaccinated against influenza could develop breakthrough disease possibly leading to hospitalisation. Costs were assigned to these health outcomes for all vaccination scenarios. This enabled the calculation of the potential costs averted or incurred as a result of switching to vaccination with an aIIV or a HD-IIV.

6.3.5 Perspective, time horizon and discounting

The CUA adopted the perspective of the Irish publicly-funded health and social care system, namely the HSE. In line with recommended good practice guidelines for the economic analysis of vaccination programmes and given the expected impact on productivity, a societal perspective was also adopted.[293] For the payer perspective, only direct medical costs to the HSE were incorporated. For the societal perspective, direct medical costs to the HSE, indirect costs such as productivity losses associated with influenza-related morbidity and mortality and the time required to care for those with influenza, and out-of-pocket expenses incurred by individuals for GP visits and medication, were included in the analysis. Costs and benefits were estimated over a single influenza season (six-month time horizon). As the time horizon of the model was less than 12 months, discounting was only applied to productivity losses associated with mortality due to influenza.[273]

In the BIA, the incremental costs and savings associated with vaccinating those aged 65 years and older with either an aIIV or a HD-IIV were estimated over a one-year time horizon. To reflect the actual cost to the HSE, and ensure consistency with national guidelines, no discounting was applied. [294]

6.3.6 Model input parameters

Probabilities, costs and QALYs were estimated from a variety of published sources, national datasets for Ireland and international datasets, including those published by the Central Statistics Office (CSO), the Healthcare Pricing Office (for Hospital In-Patient Enquiry (HIPE) data), the Health Protection Surveillance Centre (HPSC) and Eurostat.

Model inputs were selected with consideration to the hierarchy of evidence, as well as generalisability to the Irish context. All economic model input parameters are provided in Appendix A6.4.

Inputs for the BIA were consistent with those used in the CUA with the exception of the addition of VAT (where applicable). Additionally, only direct costs were included and indirect costs, such as productivity gains associated with morbidity or mortality, were excluded from the BIA.

Health outcomes – influenza

The total number of notified cases of influenza (by age group, year and vaccine type) was obtained from the epidemiological model output. It was assumed that a portion of all notified cases develop severe disease requiring hospitalisation. The probability of hospitalisation among notified cases of influenza was estimated from data from the HPSC reporting notified cases and HIPE discharge data for the years 2018, 2019, 2020 and 2022 inclusive (Table 6.3). Data from 2021 were excluded due to the impact of COVID-19. The HIPE data included the total number of inpatient discharges with a principal diagnosis of influenza (from a specified list of influenza diagnosis codes – Chapter 3) by age group and year. Based on the results from Chapter 4, there is evidence that aIIV leads to a reduction in influenza-related hospitalisations (laboratory confirmed) relative to standard IIV in adults aged 65 years and older. The relative vaccine effectiveness of aIIV (versus standard IIV) in preventing hospitalisation was estimated at 59.2% (95% CI: 14.6 to 80.5%). Hospitalisation rates for aIIV were adjusted accordingly in the model. Based on the results from Chapter 4, HD-IIV was not associated with a statistically significant reduction in influenza-related hospitalisations relative to standard IIV. However, given that the confidence bounds for the point estimate narrowly crossed the line of no effect, a pro-rata reduction in hospitalisations was allowed in the model. That is, relative to standard IIV, a 24% reduction in incidence of laboratory-confirmed influenza was associated with a corresponding 24% reduction in hospitalisation.

Table 6.3 Estimated probability of influenza-related hospitalisation among notified cases given a HSE Seasonal Influenza Vaccination Programme offering adjuvanted inactivated influenza vaccines to those aged 65 years and older

Age group (years)	Estimated probability of hospitalisation for notified influenza		
	Mean (%)	Minimum (%)	Maximum (%)
0-17	27.6	16.9	32.9
18-49	17.5	12.3	25.2
50-64	34.7	24.7	46.0
65-69	38.4	31.8	54.7
70-74	38.4	31.8	54.7
≥75	38.4	30.1	48.9

Source: HPSC notified case data[295] and HIPE discharge data (outlined in Chapter 3; Section 3.4.2).

Health outcomes – safety of enhanced inactivated influenza vaccines

With respect to serious adverse events, the assessment of the safety of enhanced IIVs (Chapter 4) demonstrated that the overall safety profiles of both aIIV and HD-IIV are comparable to that of standard IIV, but that there is an increased risk of local and systemic reactions with both aIIV and HD-IIV compared with standard IIV. While the identified safety data were considered broadly applicable to the population aged 65 years and older, there were limited data to support subgroup analysis for this cohort. This increased risk and the associated impact on quality of life was incorporated into the model. The systemic reactions with the highest relative risk for each of the enhanced IIVs (versus standard IIV) were used in the CUA, focusing on published evidence specific to the cohort aged 65 years and older (Table 6.4).

Table 6.4 Relative risk of systemic reactions for enhanced inactivated influenza vaccines, versus standard inactivated influenza vaccine, in those aged 65 years and older

Vaccine	Systemic reaction	Relative risk (95% CI) (versus standard IIV)
aIIV	Vomiting	1.48 (1.10 to 1.98)[10]
HD-IIV	Combined systemic reactions	1.19 (1.09 to 1.31)[10]

Key: aIIV – adjuvanted inactivated influenza vaccine; CI – confidence interval; HD-IIV – high-dose inactivated influenza vaccine.

Quality of life estimates

In the model, health benefits are expressed in terms of quality-adjusted life years (QALYs) gained. QALYs reflect the impact of an intervention on patients' quality and length of life, estimated using self-reported utilities or health-related quality of life.

The cohort was assigned Irish baseline utility values (by age group) at the outset of the model.[296] Each health state was associated with different health utilities to capture the impact of that state on health-related quality of life. A comprehensive search was conducted to identify original studies that elicited health state utility values or disutilities associated with influenza for both outpatients and inpatients. Preference was given to utility values measured using generic preference-based measures such as the EQ-5D.

The baseline and health state utility values used to estimate QALYs in the CUA are presented in Table 6.5. For the purpose of the CUA, it was assumed that notified cases of influenza experience seven days' utility loss due to influenza. For those hospitalised due to influenza, it was assumed that the duration of utility loss is the sum of the duration of utility loss for non-hospitalised cases (seven days) and the duration (in days) of their stay in hospital (ranging from three days for those aged 0 to 17 years, to 12 days for those aged 75 years and older). It was assumed those who experience local and systemic reactions experience influenza-related utility loss for one day.

Table 6.5 Baseline and health-state utility values for notified influenza

Age group (years)	Baseline*	Non-hospitalised influenza		Hospitalised influenza	
		Mean†	95% CI	Mean†	95% CI
0-17	0.9800	0.5700	0.4568 – 0.6796	0.4400	0.3548 – 0.5270
18-49	0.9477	0.4878	0.3926 – 0.5834	0.3533	0.2857 – 0.4240
50-64	0.9031	0.5431	0.4360 – 0.6483	0.3231	0.2615 – 0.3880
65-69	0.8790	0.5590	0.4483 – 0.6668	0.3190	0.2582 – 0.3831
70-74	0.8790	0.5590	0.4483 – 0.6668	0.3190	0.2582 – 0.3831
≥75	0.8790	0.5210	0.4187 – 0.6224	0.2810	0.2276 – 0.3376

Key: CI – confidence interval.
*Source: Irish baseline utility values – Hobbins et al.[296]
†Source: estimated based on influenza disutility values – Hollmann et al.[297] Health-state utility values for influenza only apply for the period an individual is in that health state.

Cost inputs

In accordance with national HTA guidelines, all costs are presented in 2023 euros (€).[273] All costs were derived from Irish sources and those from years prior to 2023 were adjusted using the Consumer Price Index for health.[298]

In the CUA, the costs associated with notified influenza from the payer perspective included the cost of GP visits for those with a GP visit or medical card, the cost of

prescription medication for those with a medical card and the cost of hospitalisation. The proportion of people with a GP visit and or medical card was sourced from HSE - Primary Care Reimbursement Service (PCRS) eligibility data as at February 2024 (Table 6.6).[299]

Table 6.6 Estimated proportion of the population eligible for a GP visit card or a medical card

Age group (years)	Proportion of population eligible for a GP visit card*	Proportion of population eligible for a medical card*
0-17	29.2%	28.8%
18-49	3.2%	21.5%
50-64	3.0%	29.0%
65-69	3.1%	38.7%
70-74	35.8%	56.9%
≥75	22.8%†	77.2%

*__Source:__ Health Service Executive.[299]
†This figure was adjusted from 28.2% to ensure that the total proportion of the population eligible for a GP visit card or medical card in these age groups did not exceed 100%.

It was assumed that all of those with notified influenza would attend their GP. In the absence of Irish-specific data, the frequency of GP visits related to notified cases of influenza and the probability of a prescription being issued were sourced from a number of international studies (Table 6.7).[300, 301] The average cost of a GP consultation for a public patient (€51.23) was sourced from a study that estimated unit costs for non-acute medical care in Ireland.[302] Based on UK data, it was estimated that of those receiving a prescription, 41% would receive a prescription for an antibiotic while 31% would be prescribed an analgesic. It was assumed that the remaining 28% would receive a prescription for antivirals, steroids and or expectorants. HSE prescribing guidelines and recommended treatment courses for upper and lower respiratory tract infections were used to identify treatment items for influenza.[303] Cost data for these items were sourced from the PCRS (https://www.sspcrs.ie/druglist/pub) and the average cost of prescription medication was estimated using relevant published guidelines (Table 6.8).[304] While it is recognised that antibiotics are not effective for treating influenza, it was assumed that some of those presenting to their GP with influenza-like symptoms may be treated with antibiotics as symptoms may be clinically similar to bacterial respiratory tract infections. Details of the items included in estimating the average cost of prescription medication for influenza for both children and adults are included in Appendix A6.5.

Table 6.7 Average number of GP visits per notified influenza case and probability prescription issued

Age group (years)	Mean GP visits	Probability prescription issued
0-17	1.13	48.1%
18-49	1.12	55.1%
50-64	1.15	55.1%
65-69	1.22	55.1%
70-74	1.22	55.1%
≥75	1.22	55.1%

Source: Meier et al. 2020[300] and Ehlken et al. 2015[301]

Table 6.8 Estimated average cost of medication for influenza

Population groups	Prescription		Over-the-counter
	Public patient*	Private patient†	All patients†
Children	€9.46	€12.78	€21.00
Adults	€8.96	€12.03	€33.00

*Used for payer perspective – see Appendix A6.5 for details of items included in estimate.
†Used for societal perspective – see Appendix A6.6 for details of items included in estimate.

The average cost of an influenza-related hospitalisation cost by age group (Table 6.9) was estimated based on the total number of HIPE discharges with a principal diagnosis of influenza for the four-year period from 2018 to 2022, excluding 2021 due to the impact of COVID-19 on overall hospitalisations.[125] The costs provided in Table 6.9 are estimated average costs and individual cases could incur higher or lower costs depending on the intensity of treatment and length of stay.

Table 6.9 Estimated cost of an influenza-related hospitalisation

Age group (years)	Estimated average hospitalisation cost for a case of influenza*
0-17	€4,618
18-49	€4,609
50-64	€4,841
65-69	€5,031
70-74	€5,231
≥75	€5,479

*__Source:__ Estimated based on DRGs provided by the Healthcare Pricing Office[125]

In addition to the costs included in the payer perspective (described above), the societal perspective also included the following costs associated with influenza:

- out-of-pocket expenses for those not eligible for a GP visit or medical card and who therefore incur GP consultation and prescription medication costs (transportation costs incurred to attend the GP were not included)
- out-of-pocket expenses for over-the-counter medications to alleviate symptoms of influenza
- productivity loss of paid work, due to absenteeism, for those who are ill with influenza and those who are caring for children who are ill.

The proportion of the population not eligible for a GP visit or medical card (and therefore considered private patients) was determined based on scheme eligibility data published by the HSE (Table 6.6).[299] The average cost of a GP consultation for private patients (€55.68) was sourced from the literature.[302] The average cost of prescription medication issued to private patients was estimated as above for public patients and based on an average of three values: the estimated cost under the Drugs Payment Scheme; an estimated cost that included 20% mark-up and a €5 fee per item for the pharmacy; and an estimated cost that included no mark-up and a €10 fee for the pharmacy. The average cost of over-the-counter medication for influenza was estimated using current retail prices (assuming a seven-day course) and data from an international study that estimated the proportion of people taking each medicine class.[305] Details of the items included in estimating the average cost of over-the-counter medication for influenza for both children and adults are included in Appendix A6.6.

Estimates of the productivity loss to society due to absence from paid work for those ill with influenza and those caring for children who are ill, were valued using the Human Capital Approach by multiplying the days lost to health problems by median daily earnings.[306] The average number of work days lost per notified influenza case that was not hospitalised was assumed to be five, equating to the number of days of utility loss due to influenza (n=7) minus two non-working days per week. The average number of work days lost per case of notified influenza that required hospitalisation was assumed to be five (as above for those not hospitalised) plus the average length of stay in hospital (ranging from three days for those aged 0 to 17 years, to 12 days for those aged 75 years and older). Labour force data published by the CSO were used to estimate the proportion of the population in paid employment for each age group of the model.[307] Earnings analysis data, published by the CSO, were used to estimate median daily earnings by age group (Table 6.10).[308]

Estimates of the productivity loss to society as a result of influenza-related mortality were also valued using the Human Capital Approach[306] and calculated using life tables, labour force and earnings data.[307-309]

Table 6.10 Proportion of the population in paid employment and estimate of median daily earnings by age group

Age group (years)	Proportion of the population working	Estimate of median daily earnings
0-17	4.9%	€70.77
18-49	78.8%	€143.18
50-64	73.0%	€149.35
65-69	26.9%	€124.09
70-74	16.9%	€124.09
≥75	4.6%	€124.09

Source: Central Statistics Office[307, 308]

Vaccination programme costs

For both the payer and societal perspectives, only the incremental cost of strategies based on aIIV and HD-IIV, over and above the cost of a strategy based on standard IIV, was included in the vaccination programme costs. It was assumed that administration and national cold chain service costs would remain unchanged. The wholesale costs of standard IIV, aIIV and HD-IIV to the healthcare system (which could, for example, include a volume discount) are not known. For the purpose of the economic evaluation, the wholesale cost of a single pre-filled syringe of standard IIV was assumed to be €10.99 (ex-VAT) based on the current list price. Based on

published prices for standard IIV, aIIV and HD-IIV in Europe[310, 311] and the vaccine prices used in the studies assessed in the rapid review of modelling studies (Chapter 5), relative vaccine prices of 1.5 and 3.25 times per dose, versus standard IIV, were assumed for aIIV and HD-IIV, respectively. This equates to €16.49 (ex-VAT) and €35.72 (ex-VAT) for a single pre-filled syringe of aIIV and HD-IIV, respectively.

6.3.7 Model outputs

In the CUA, incremental costs and QALYs were estimated and then used to calculate a cost-effectiveness ratio – the incremental cost per QALY gained. In the first instance, vaccination strategies using aIIV and HD-IIV for those aged 65 years and older were compared with vaccination using standard IIV to estimate an average cost-effectiveness ratio (ACER). The strategies were then ordered by increasing cost and compared with the previous least costly alternative to estimate an incremental cost-effectiveness ratio (ICER). In accordance with national HTA guidelines, the ICERs were reported relative to willingness-to-pay (WTP) thresholds of €20,000 and €45,000 per QALY.[273] For the BIA, the incremental costs associated with and costs averted as a result of the introduction of aIIV and HD-IIV for those aged 65 years and older were estimated and used to calculate the incremental budget impact over one year.

6.3.8 Assessment and quantification of uncertainty

Probabilistic and deterministic sensitivity analyses (PSA and DSA, respectively) were conducted to test the robustness of the economic model outputs.

Sensitivity analysis for cost-utility analysis

Parameter uncertainty was assessed using a Monte Carlo simulation with 10,000 iterations. Each model parameter was defined by a statistical distribution to represent uncertainty in the mean parameter value. For each parameter, an appropriate statistical distribution was selected (for example, a beta distribution for a probability). Parameter values were then drawn as random variates from their specified distributions and the total costs and benefits were recalculated.

The total costs and QALYs for each simulation were recorded and used to quantify the proportion of simulations that were considered cost effective with respect to an illustrative WTP threshold (that is, €45,000 per QALY). The output was presented on a cost-effectiveness plane. While there is no specific guidance available on the optimal number of simulations necessary to reach convergence,[312] model convergence was assessed after 10,000 simulations.

One-way sensitivity analysis (OWSA) for each vaccination strategy was conducted by selecting the PSA simulations where each of the parameter values were at their

lowest and highest 5% of values and estimating the mean incremental costs and QALYs for those simulations. The impact of extreme variation in single input parameters on the model output was presented on a tornado plot. This provides a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters.

Sensitivity analysis for budget impact analysis

One-way sensitivity analysis for the BIA was also conducted by selecting the PSA simulations where each of the parameter values were at their lowest and highest 5% of values and estimating the mean incremental budget impact for those simulations. The impact of extreme variation in single input parameters on the model output was examined to assess the sensitivity of the model to the uncertainty associated with individual parameters.

Scenario analysis for economic model

In developing the economic model, important assumptions were made regarding parameter uncertainty related to the unit cost of standard IIV and the relative price (compared with standard IIV) of the enhanced IIVs. The relative vaccine prices used in the studies reported in Chapter 5, and where publicly available, demonstrated considerable variability. Scenario analysis was conducted to assess these uncertainties, whereby the base-case parameter values for the unit cost of standard IIV and the relative price of aIIV and HD-IIV (compared with standard IIV) were varied.

Model calibration and validation

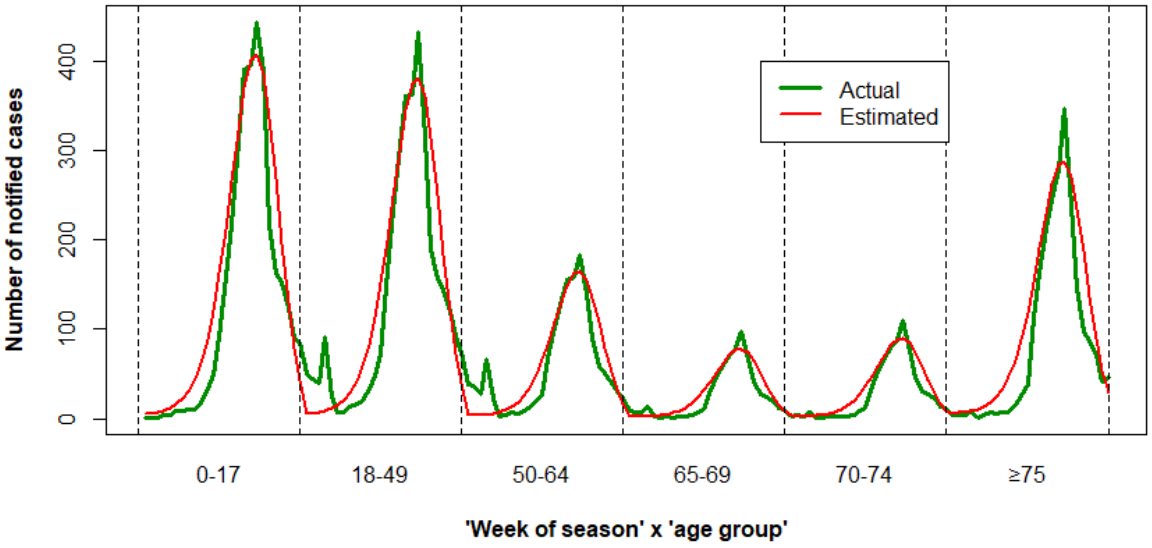
Internal validation of the economic model was conducted in accordance with HIQA's Internal Quality Assurance Framework. All model inputs, calculations, and model outputs were reviewed by a second economic modeller.

6.4 Results

6.4.1 Epidemiological analysis

The incidence of notified influenza disease in Ireland estimated by the epidemiological model, before vaccination with an enhanced IIV for those aged 65 years and older was introduced to the model, approximated an average influenza season based on published influenza notification data (Figure 6.2 and Appendix A6.3).[295] Results from the epidemiological analysis indicated that the estimated number of notified influenza cases across all ages would be 11,845 (95% CI: 7,954 to 15,684) in an average influenza season. The number of observed cases ranged from 7,305 in the 2018/2019 season to 15,472 in the 2022/2023 season, while the number of estimated cases ranged from 8,055 in the 2018/2019 season to 16,564 in the 2022/2023 season.

Figure 6.2 Observed and estimated (from epidemiological model) incidence of notified influenza in an average influenza season



Based on the findings in Chapter 4, HD-IIV demonstrated increased clinical effectiveness, compared with standard IIV, in preventing influenza disease in those aged 65 years and older. Following the introduction of HD-IIV to the epidemiological model, the predicted reduction in notified influenza cases in a single average influenza season was 43.6% for the population as a whole and 52.6% in those aged 65 years and older (Table 6.11).

Table 6.11 Estimated change (%) (based on the epidemiological model output) in notified influenza cases associated with using a strategy with high-dose compared with standard inactivated influenza vaccine in those aged 65 years and older

Age group (years)	Mean	LCI	UCI
0-17	-38.2%	-20.1%	-53.2%
18-49	-40.0%	-21.2%	-55.3%
50-64	-41.7%	-22.3%	-57.4%
65-69	-48.2%	-26.5%	-64.9%
70-74	-52.3%	-29.2%	-69.3%
≥75	-53.9%	-30.2%	-70.8%
≥65	-52.6%	-29.3%	-69.6%
All	-43.6%	-23.5%	-59.5%

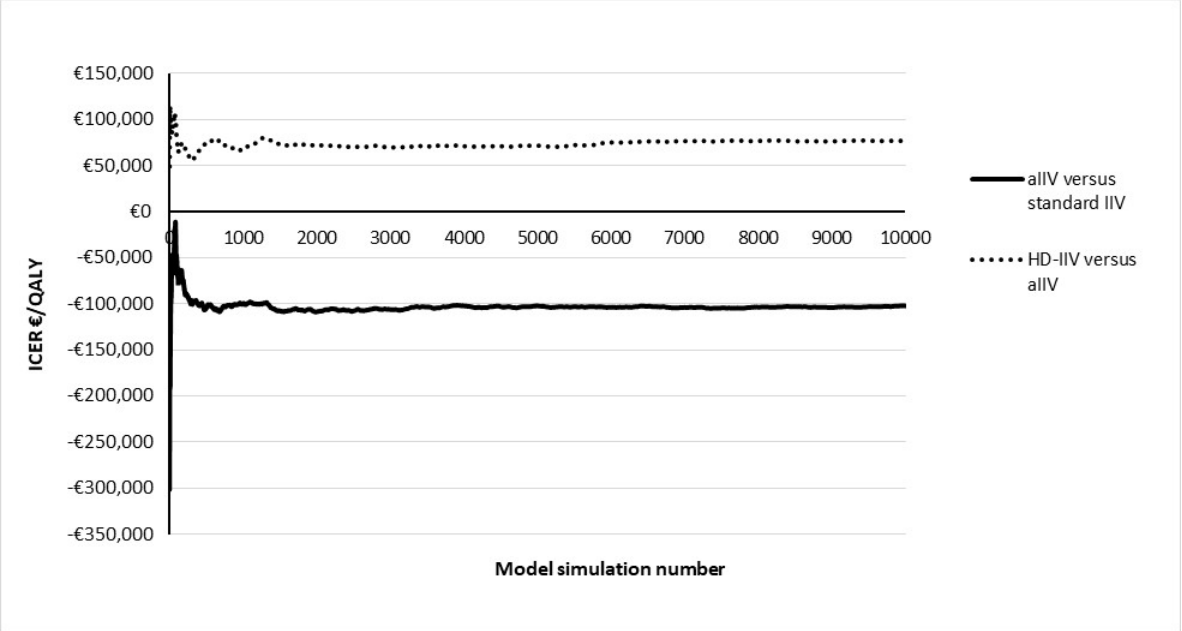
Key: LCI – lower confidence interval; UCI – upper confidence interval.

6.4.2 Cost-utility analysis

Base-case analysis

The reported incremental cost-effectiveness ratio (ICER) reflects the mean ICER obtained by PSA with 10,000 simulations, comprising 40 economic simulations for each of the 250 simulations generated by the epidemiological model (Section 0). Convergence testing indicated that the number of simulations was sufficient to provide a stable result. For both vaccination strategies under consideration, a stable estimate of the ICER was achieved after approximately 2,000 simulations (Figure 6.3).

Figure 6.3 Model convergence by vaccination strategy



Key: aIIV – adjuvanted inactivated influenza vaccine; HD-IIV – high-dose inactivated influenza vaccine; QALY – quality-adjusted life year; IIV – inactivated influenza vaccine; ICER – incremental cost-effectiveness ratio.

Overall, both aIIV and HD-IIV strategies were more effective than the existing standard IIV strategy, generating incremental QALY gains. However, a strategy based on aIIV was less costly than one based on standard IIV, while a strategy based on HD-IIV was more costly than both standard IIV and aIIV-based strategies. Incremental cost-effectiveness ratios (ICERs) were estimated by ordering the vaccination strategies by increasing cost (Table 6.12) and comparing each strategy with the preceding least costly strategy. Accordingly, the incremental analysis below compared a strategy based on aIIV with a strategy based on standard IIV while a strategy based on HD-IIV was compared with a strategy based on aIIV. From the payer perspective, over a six-month time horizon, it was estimated that:

- A strategy based on aIIV would dominate standard IIV (using current list price of €10.99 (ex-VAT) per dose for standard IIV), being less costly and more effective, generating an incremental cost saving of €1.1 million and a gain of 10 QALYs. A strategy based on aIIV could thus be considered cost saving relative to the existing standard-IIV-based strategy.
- A strategy based on HD-IIV would be associated with an incremental cost of €8.8 million and an incremental gain of 114 QALYs, when compared with a strategy based on aIIV, producing an ICER of €76,731 per QALY. As such, it would be considered not cost effective, at a willingness to pay threshold of €45,000 per QALY.

Table 6.12 Results of probabilistic sensitivity analysis

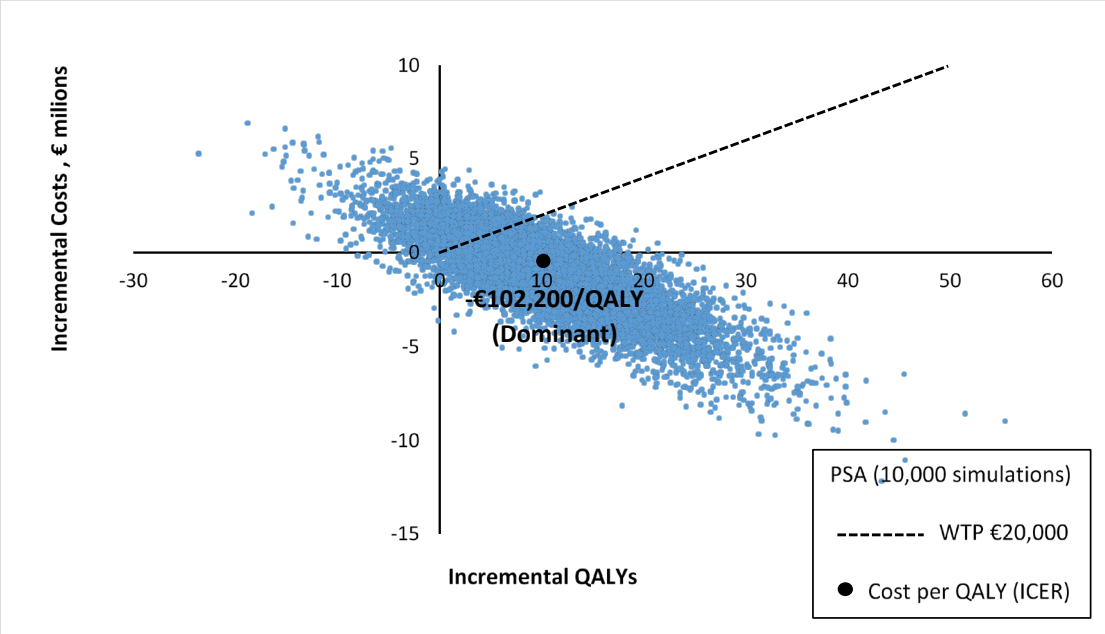
Vaccine	Total Costs (€, million)	Total QALYs	ACER† (€/QALY)	Incremental Costs (€, million) for ICER (95% CI)	Incremental QALYs for ICER (95% CI)	ICER† (€/QALY) (95% CI)
Standard	24.0	2,468,281	-	-	-	-
aIIV	22.9	2,468,292	Dominant	-1.1 (-5.7 to 2.7)	10 (-4 to 28)	Dominant
HD-IIV	31.7	2,468,406	61,763	8.8 (0.3 to 17.6)	114 (15 to 203)	76,731

Key: aIIV – adjuvanted inactivated influenza vaccine; ACER – average cost-effectiveness ratio; HD-IIV – high-dose inactivated influenza vaccine; ICER – incremental cost-effectiveness ratio; IIV – inactivated influenza vaccine; QALY – quality-adjusted life year.

†ACER compares each vaccination strategy with no vaccination. ICER compares each vaccination strategy with the previous least costly strategy.

The cost-effectiveness plane comparing a strategy based on aIIV with the existing standard IIV based strategy is presented in Figure 6.4. A total of 67% of the 10,000 simulations lie in the south-east quadrant of the cost-effectiveness plane (aIIV strategy is more effective and less costly than standard IIV strategy). A further 2% of all simulations lie below the WTP threshold of €20,000 per QALY in the north-east quadrant of the cost-effectiveness plane (aIIV strategy is more costly and more effective than standard IIV strategy).

Figure 6.4 Cost-effectiveness plane for a strategy based on adjuvanted versus standard inactivated influenza vaccine

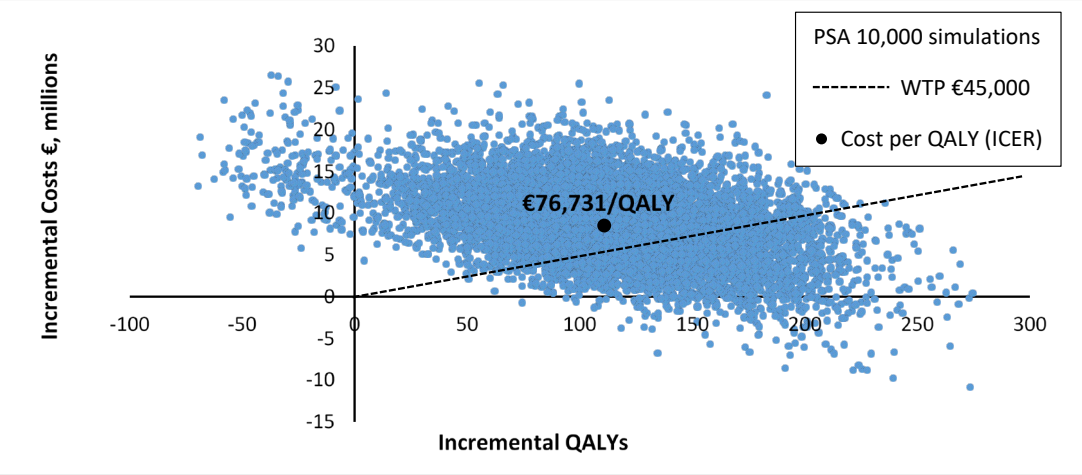


Key: ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; WTP – willingness-to-pay.

The cost-effectiveness plane comparing a strategy based on HD-IIV with one based on aIIV is presented in Figure 6.5. A total of 73% of the 10,000 simulations lie

above the willingness-to-pay threshold of €45,000 per QALY in the north-east quadrant of the cost-effectiveness plane (HD-IIV strategy is more costly and more effective than aIIV strategy).

Figure 6.5 Cost-effectiveness plane for a strategy based on high-dose versus adjuvanted inactivated influenza vaccine

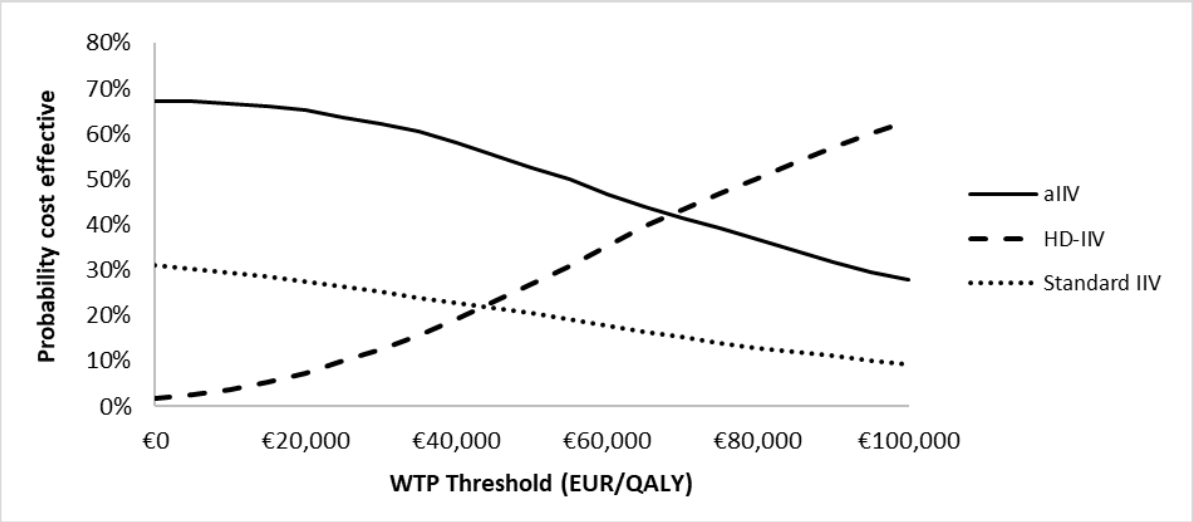


Key: ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; WTP – willingness-to-pay.

When the CUA was considered from the societal perspective, the results were consistent with those from the payer perspective. A strategy based on aIIV dominated SD-IIV, being more effective and less costly. While a strategy based on HD-IIV provided an additional QALY gain relative to an aIIV based strategy, it was also more expensive with an ICER of €55,642 per QALY.

The cost-effectiveness acceptability curve (CEAC) summarises the uncertainty in the results of the economic evaluation. It plots the likelihood that each of the alternative strategies under consideration has the greatest net monetary benefit (that is, the intervention's value in monetary terms) across a range of WTP thresholds. From the payer perspective and at a WTP threshold of €20,000 per QALY, the probability of a strategy based on aIIV being the cost-effective strategy was 65.2% and the probability of the existing standard IIV based strategy being the cost-effective strategy was 27.6%. At a WTP threshold of €45,000 per QALY, the probability of a strategy based on aIIV being the cost-effective strategy was 55.4% while the probability of HD-IIV and standard-IIV-based strategies being the cost-effective strategies was 22.9% and 21.7%, respectively (Figure 6.6).

Figure 6.6 Cost-effectiveness acceptability curve



Key: aIIV – adjuvanted inactivated influenza vaccine; HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; QALY – quality-adjusted life year; WTP – willingness-to-pay.

One-way sensitivity analysis

For the one-way sensitivity analysis (OWSA), a number of input parameters from the epidemiological model (vaccine effectiveness of standard IIV for three separate age groups and the relative vaccine effectiveness of HD-IIV (versus standard IIV) in preventing influenza in those aged 65 years and over) and all parameters from the economic model were varied and ranked in order of increasing influence on uncertainty in the ICERs. The analysis was conducted for each parameter and each vaccination strategy by identifying the PSA simulations with the lowest 5% and highest 5% parameter values, estimating the mean incremental costs and QALYs for these simulations and calculating the associated ICERs.

Results are presented as tornado plots which provide a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters. Only those parameters that result in a variation of at least 10% from the base-case ICER are presented.

<u>Adjuvanted compared with standard inactivated influenza vaccine strategies</u>

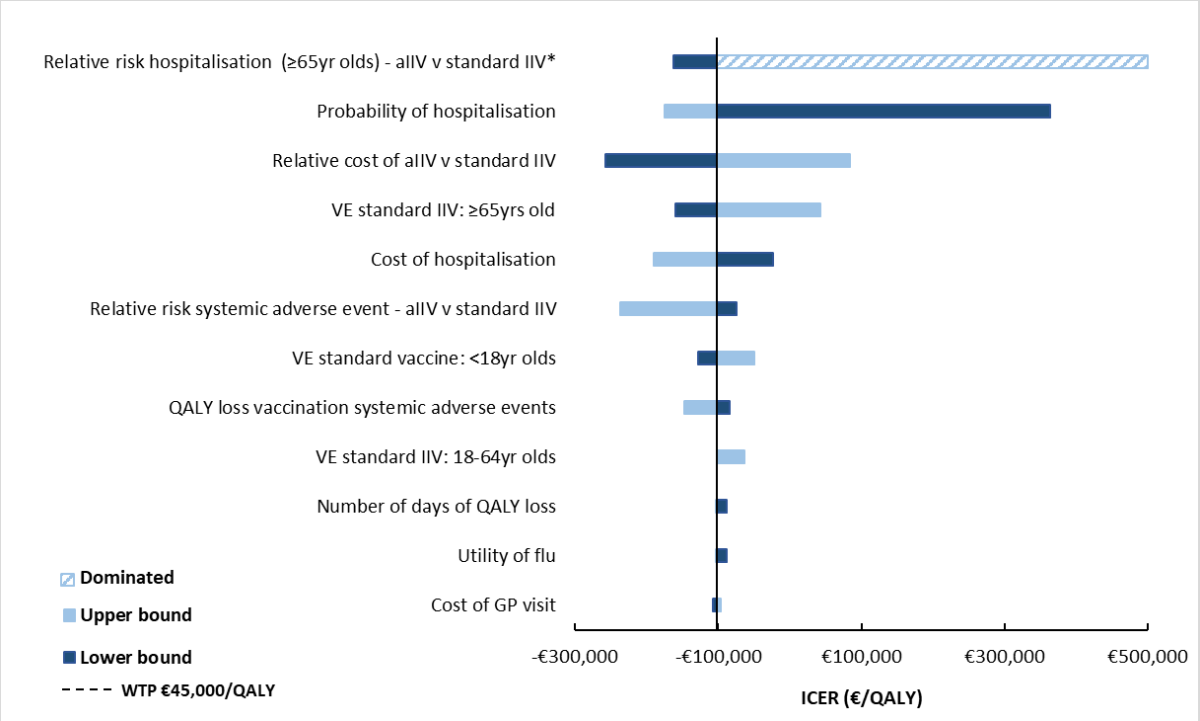
The results of the OWSA demonstrated that the ICER for a strategy involving offering those aged 65 years and older, an aIIV compared with a standard IIV was most sensitive to the following parameters:

- relative risk of hospitalisation with aIIV versus standard IIV in those aged 65 years and older
- probability of hospitalisation for influenza
- relative cost of aIIV versus standard IIV

- effectiveness of standard IIV in those aged 65 years and older.

For all four parameters, the ICERs at either the lower or upper bound of parameter values were above or close to the WTP threshold of €45,000 per QALY. At the upper bound of parameter values for the relative risk of hospitalisation, a strategy based on aIIV was more costly and less effective than one based on standard IIV. At the lower bound of parameter values for the probability of hospitalisation, the mean ICER for aIIV was €363,200 per QALY. At the upper bound of parameter values for the relative cost of aIIV, the mean ICER for a strategy based on aIIV was €83,503 per QALY. At the upper bound of parameter values for the vaccine effectiveness of standard IIV, the mean ICER for a strategy based on aIIV was €42,411 per QALY (Figure 6.7).

Figure 6.7 Tornado plot of one-way sensitivity analysis for strategy based on adjuvanted compared with standard inactivated influenza vaccine



Key: aIIV – adjuvanted inactivated influenza vaccine; HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year; VE – vaccine effectiveness; WTP – willingness-to-pay.
* At the upper bound level, aIIV was dominated (more costly and less effective) by standard IIV.

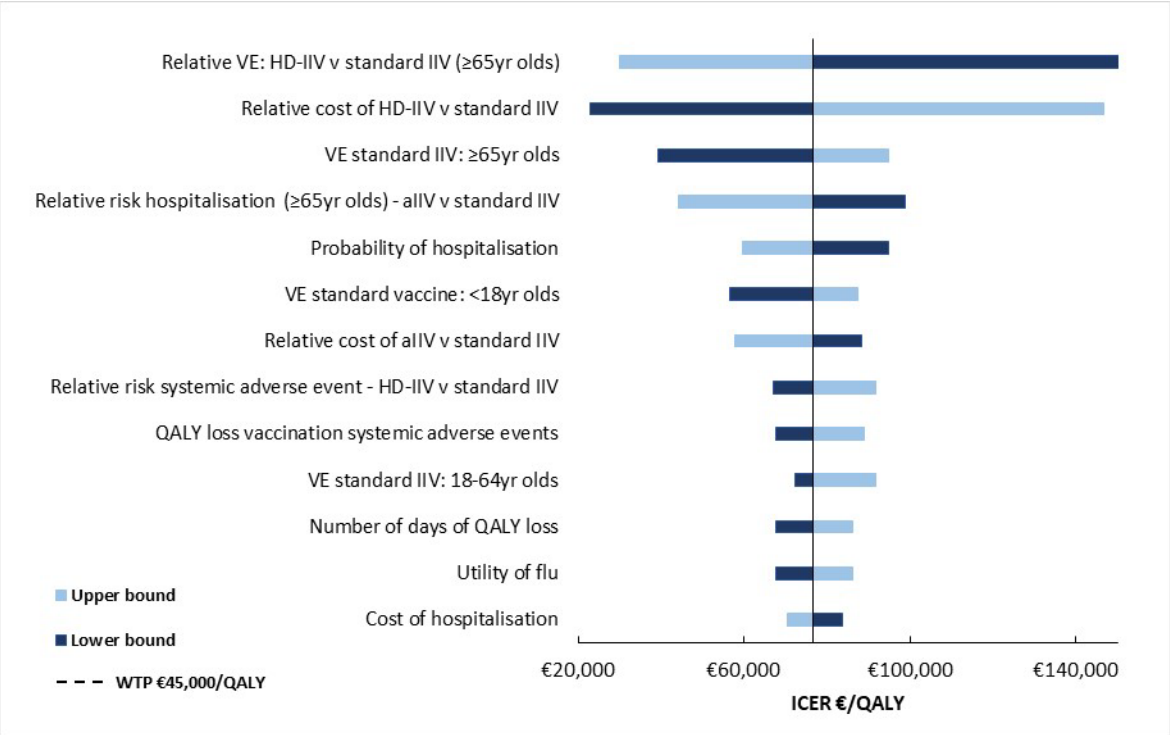
High-dose inactivated influenza vaccine compared with adjuvanted inactivated influenza vaccine

The results of the OWSA demonstrated that the ICER for a strategy involving vaccinating those aged 65 years and older with a HD-IIV compared with aIIV was most sensitive to the following parameters:

- relative cost of HD-IIV versus standard IIV
- relative vaccine effectiveness of HD-IIV versus standard IIV in preventing influenza in those aged 65 years and older
- vaccine effectiveness of standard IIV in those aged 65 years and older
- relative risk of hospitalisation with aIIV versus standard IIV in those aged 65 years and older.

For all four parameters, the mean ICER for a strategy based on HD-IIV, relative to one based on aIIV, at either the lower or upper bound of parameter values, was below the WTP threshold of €45,000 per QALY. At the lower bound of parameter values for the relative cost of HD-IIV, versus standard IIV, the mean ICER was €22,924 per QALY. At the upper bound of parameter values for the relative vaccine effectiveness of HD-IIV, versus standard IIV, the mean ICER was €30,078 per QALY. At the lower bound of parameter values for the vaccine effectiveness of standard IIV, the mean ICER was €39,228 per QALY. At the upper bound of parameter values for the relative risk of hospitalisation with aIIV, versus standard IIV, the mean ICER was €44,196 per QALY (Figure 6.8).

Figure 6.8 Tornado plot of one-way sensitivity analysis comparing strategies based on high-dose and adjuvanted inactivated influenza vaccines



Key: aIIV – adjuvanted inactivated influenza vaccine; HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year; VE – vaccine effectiveness; WTP – willingness-to-pay.

Scenario analysis for cost-utility analysis

In developing the economic model, important assumptions were made regarding the parameter values for the relative cost of a pre-filled syringe (ingredient cost of a single dose) of the enhanced IIVs versus standard IIV. The results of the OWSA highlighted the uncertainty associated with these parameter values and therefore scenario analysis was conducted to further assess this uncertainty and the impact on the results of the cost-utility analysis. The unit costs of the three vaccines were varied simultaneously and the strategies with the largest net monetary benefit at WTP thresholds of €20,000 and €45,000 per QALY were identified. The following assumptions were used in the scenario analysis:

- the unit cost of standard IIV would not be higher than the current list price (€10.99, ex-VAT)
- the unit cost of standard IIV would always be lower than that of aIIV
- the unit cost of aIIV would always be lower than that of HD-IIV.

Based on unit costs ranging from €5 to €10.99 for standard IIV, €10.99 to €25 for aIIV, and €10.99 to €45 for HD-IIV, the results indicate that:

- Where the difference in unit cost between aIIV and standard IIV was €8 or less, at a WTP threshold of €20,000 per QALY, a strategy with aIIV generated the largest net monetary benefit.
- Where the difference in unit cost between aIIV and standard IIV was between €8 and €9, there remains a high degree of uncertainty as to whether a strategy with standard IIV or aIIV would generate the largest net monetary benefit.
- Where the difference in unit cost between aIIV and standard IIV was €9 or more, at a WTP threshold of €20,000 per QALY, a strategy with standard IIV generated the largest net monetary benefit.
- A strategy with HD-IIV would generate the largest net monetary benefit only where the difference in cost between it and aIIV was €9 or less.

The full set of results for WTP thresholds of €20,000 and €45,000 per QALY are presented in the matrices in Figure 6.9 and Appendix A6.7, respectively.

Figure 6.9 Scenario analysis results for largest net monetary benefit of all three vaccination strategies at a willingness-to-pay threshold of €20,000 per QALY, by unit cost of vaccine

Vaccination strategy with the largest net monetary benefit at a willingess-to-pay threshold of €20,000 per QALY									
		High-dose IIV							
Standard IIV	Adjuvanted IIV	€15.00	€20.00	€25.00	€30.00	€35.00	€36.27	€40.00	€45.00
€5.00	€10.99	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€5.00	€12.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€5.00	€14.00	High-dose	High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€16.00		High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€16.49		High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€18.00		High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€20.00			Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€22.00			Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€24.00			Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€25.00				Standard	Standard	Standard	Standard	Standard
€7.50	€10.99	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€12.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€14.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€16.00		High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€7.50	€16.49		High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€7.50	€18.00		High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€7.50	€20.00			High-dose	Standard	Standard	Standard	Standard	Standard
€7.50	€22.00			High-dose	Standard	Standard	Standard	Standard	Standard
€7.50	€24.00			High-dose	Standard	Standard	Standard	Standard	Standard
€7.50	€25.00				Standard	Standard	Standard	Standard	Standard
€10.00	€10.99	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€12.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€14.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€16.00		High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€16.49		High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€18.00		High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€20.00			High-dose	Standard	Standard	Standard	Standard	Standard
€10.00	€22.00			High-dose	Standard	Standard	Standard	Standard	Standard
€10.00	€24.00			High-dose	Standard	Standard	Standard	Standard	Standard
€10.00	€25.00				Standard	Standard	Standard	Standard	Standard
€10.99	€12.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€14.00	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€16.00		High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€16.49		High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€18.00		High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€20.00			High-dose	Standard	Standard	Standard	Standard	Standard
€10.99	€22.00			High-dose	Standard	Standard	Standard	Standard	Standard
€10.99	€24.00			High-dose	Standard	Standard	Standard	Standard	Standard
€10.99	€25.00				Standard	Standard	Standard	Standard	Standard

Key: IIV – inactivated influenza vaccine.

Indicates results of base-case scenario.

Using the base-case cost of €10.99 (ex-VAT) for a single pre-filled syringe of standard IIV, the base-case parameter values for both enhanced IIVs were also varied simultaneously. The resulting ICERs for strategies involving HD-IIV (compared with aIIV) at varying vaccine costs are presented in Table 6.13. At a base-case price of €10.99 for standard IIV, it was estimated that the ICER for a strategy based on HD-IIV (compared with aIIV) would fall below the WTP threshold of €45,000 per

QALY when the difference in vaccine price between HD-IIV and aIIV was approximately €15. It was estimated that the ICER for a strategy based on HD-IIV (compared with aIIV) would fall below the WTP threshold of €20,000 per QALY when the difference in vaccine price between HD-IIV and aIIV was approximately €10.00.

Table 6.13 Incremental cost-effectiveness ratios (€/QALY) for strategies involving high-dose compared with adjuvanted inactivated influenza vaccine by vaccine cost†

		Unit cost of aIIV (€) (ex-VAT)							
		10.99	12.00	14.00	16.00	18.00	20.00	22.00	25.00
Unit cost of HD-IIV (€) (ex-VAT)	10.99	-31,465	-36,394	-46,154	-55,914	-65,674	-75,434	-85,194	-99,834
	15.00	-11,897	-16,825	-26,585	-36,345	-46,105	-55,865	-65,625	-80,265
	20.00	12,503	7,574	-2,186	-11,945	-21,705	-31,465	-41,225	-55,865
	25.00	36,903	31,974	22,214	12,454	2,694	-7,066	-16,825	-31,465
	30.00	61,303	56,374	46,614	36,854	27,094	17,334	7,574	-7,066
	35.00	85,702	80,774	71,014	61,254	51,494	41,734	31,974	17,344
	40.00	110,102	105,173	95,414	85,654	75,894	66,134	56,374	41,734
	45.00	134,502	129,573	119,813	110,053	100,294	90,534	80,774	66,134

Key: aIIV – adjuvanted inactivated influenza vaccine; HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; VAT – value-added tax.

†Assumes unit cost of €10.99 (ex-VAT) for standard IIV.

Indicates HD-IIV strategy is cost saving compared with aIIV strategy.

Indicates ICER for HD-IIV, versus aIIV strategy, is below WTP threshold of €25,000 per QALY.

Indicates ICER for HD-IIV, versus aIIV strategy, is between WTP threshold of €25,000 and €45,000 per QALY.

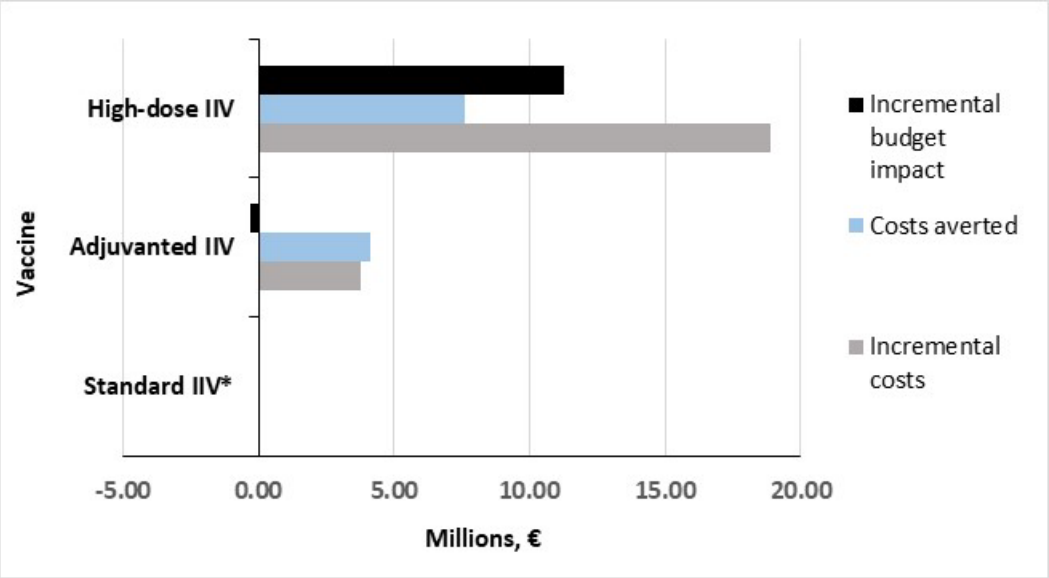
Indicates ICER for HD-IIV, versus aIIV strategy, is above WTP threshold of €45,000 per QALY.

Closest approximation to ICER when the unit costs of HD-IIV and aIIV are set at their base-case values.

6.4.3 Budget impact analysis

The estimated eligible population for the BIA was the population aged 65 years and older (approximately 806,000 persons).[287] In the first instance, the BIAs for strategies involving aIIV and HD-IIV are presented relative to the existing strategy of standard IIV, followed by an analysis of the incremental budget impact of a HD-IIV versus aIIV strategy. The costs incurred are limited to the incremental cost of an enhanced IIV strategy over and above the cost of the existing strategy of standard IIV. It was assumed that vaccination coverage rates, and vaccine administration and national cold chain service costs would not differ between vaccination strategies. In line with national guidelines,[273] VAT is included in the BIA. VAT on non-oral drugs (such as injectables) is standard rated, (23% as of March 2024).[313]

Figure 6.10 Incremental budget impact of adjuvanted and high-dose inactivated influenza vaccine strategies versus the standard inactivated influenza vaccine strategy



Key: IIV – inactivated influenza vaccine.
*The incremental budget impact for standard IIV is €0.00 as it is the comparator.

Base-case analysis for adjuvanted inactivated influenza vaccine strategy compared with standard inactivated influenza vaccine strategy

Assuming a vaccine price of €10.99 + VAT for standard IIV and a relative vaccine price of 1.5 times for aIIV (price of €16.49 + VAT), the one-year incremental budget impact of aIIV was estimated at -€316,000 although this was associated with substantial uncertainty (95% CI: -€5.1 million to €3.6 million). Increased expenditure on procurement of the aIIV (€3.8 million) was offset by savings in the cost of hospitalisation (€4.1 million) due to the higher clinical effectiveness of aIIV (compared with standard IIV) in reducing influenza-related hospitalisation in those aged 65 years and older (Figure 6.10).

One-way sensitivity analysis for adjuvanted inactivated influenza vaccine strategy compared with standard inactivated influenza vaccine strategy

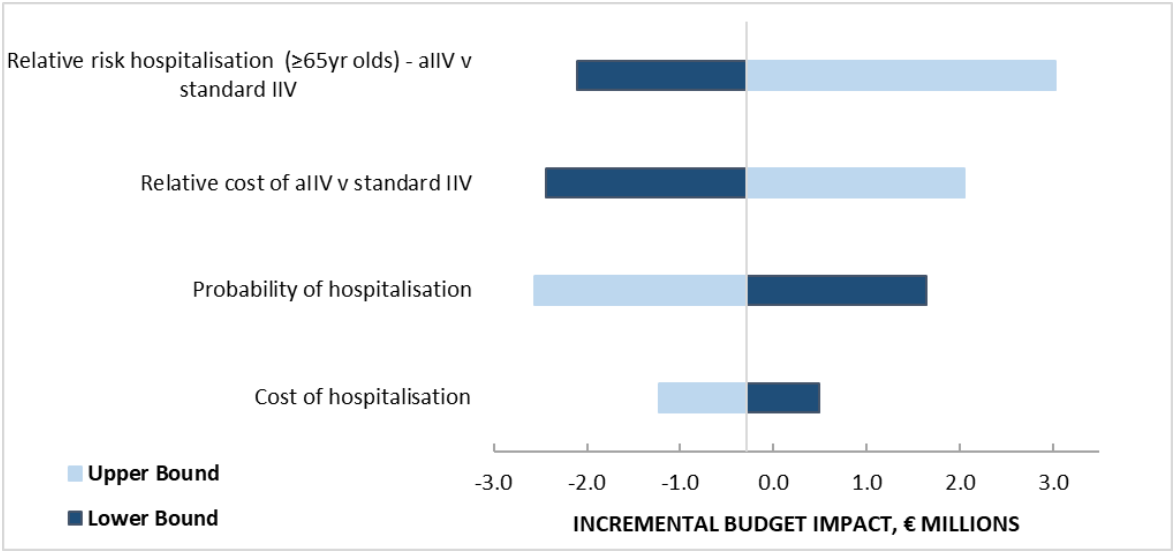
As in the CUA, OWSA was undertaken to assess the impact of variations in input parameters on the budget impact of aIIV. All parameters from the economic model were varied and ranked in order of increasing influence on uncertainty in the budget impact. The analysis was conducted for each parameter by identifying the PSA simulations with the lowest 5% and highest 5% parameter values and estimating the mean incremental budget impact for these simulations.

The BIA for a strategy based on aIIV compared with the existing standard IIV-based strategy was sensitive to the following parameters:

- relative risk of hospitalisation with aIIV versus standard IIV in those aged 65 years and older
- relative cost of aIIV versus standard IIV
- probability of hospitalisation for influenza
- cost of hospitalisation.

For all four parameters, the OWSA highlighted that a strategy based on aIIV (compared with standard IIV) changed from a cost saving (range -€1.2 to -€2.6 million) to an incremental cost (range €0.5 to €3.0 million) when the parameter values were set at either the lower or upper bound. Specifically, the upper bound of parameter values for the relative risk of hospitalisation the mean incremental budget impact was €3.0 million. At the upper bound of parameter values for the relative cost of the vaccines, the mean incremental budget impact was €2.1 million. At the lower bound of parameter values for the probability of hospitalisation, the mean incremental budget impact was €1.6 million. At the lower bound of parameter values for the cost of hospitalisation, the mean incremental budget impact was €0.5 million (Figure 6.11).

Figure 6.11 Tornado plot of one-way sensitivity analysis for budget impact comparing adjuvanted with standard inactivated influenza vaccine strategies



Key: aIIV – adjuvanted inactivated influenza vaccine; IIV – inactivated influenza vaccine.

Base-case analysis for high-dose inactivated influenza vaccine strategy compared with standard inactivated influenza vaccine strategy

Assuming a vaccine price of €10.99 + VAT for standard IIV and a relative vaccine price of 3.25 times for HD-IIV (price of €35.72 + VAT), the one-year incremental budget impact of a strategy based on HD-IIV was estimated at €11.3 million (95% CI 0.7 million to 22.1 million) (Figure 6.10). Increased spending on procurement of

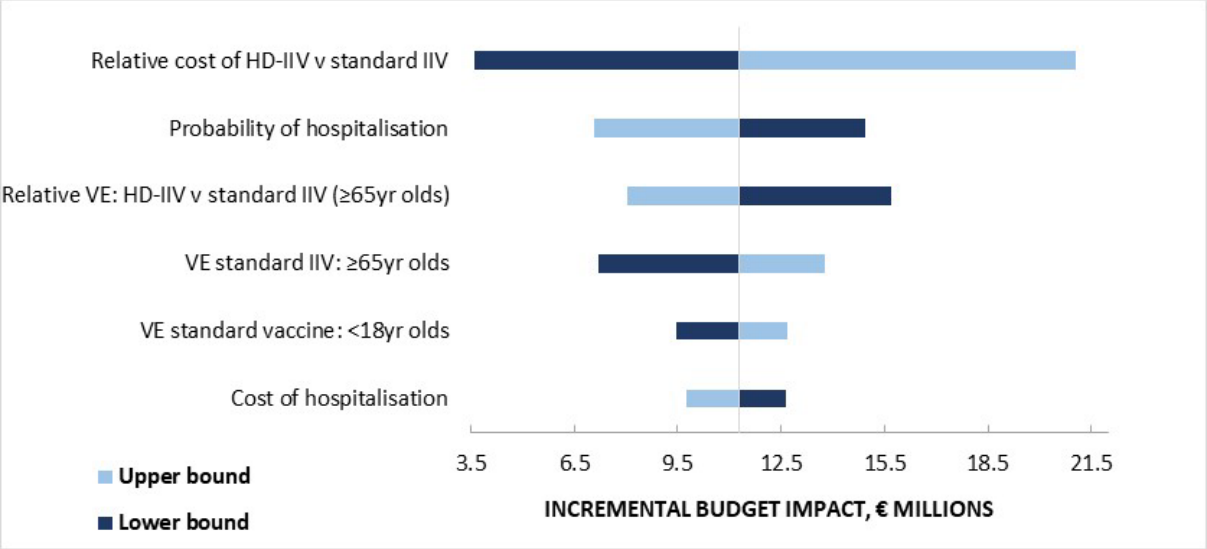
HD-IIV (€18.9 million) was partially offset by cost savings (€7.6 million) from reductions in hospitalisations, GP visits and prescription medication for those with GP visit or medical cards, due to the higher clinical effectiveness of HD-IIV, compared with standard IIV, in preventing influenza.

The results of the OWSA demonstrated that the BIA for HD-IIV compared with standard IIV was most sensitive to the following parameters:

- relative cost of HD-IIV versus standard IIV
- probability of hospitalisation for influenza
- relative vaccine effectiveness of HD-IIV versus standard IIV in preventing influenza in those aged 65 years and older
- vaccine effectiveness of standard IIV in preventing influenza in those aged 65 years and older
- vaccine effectiveness of standard vaccine in preventing influenza in those aged less than 18 years
- cost of hospitalisation.

In the OWSA, the incremental budget impact for a strategy based on HD-IIV (compared with standard IIV) across all five parameters ranged from €3.6 million at the lower bound of parameter values for the relative cost of HD-IIV (versus standard IIV) to €21 million at the upper bound of the same parameter value (Figure 6.12).

Figure 6.12 Tornado plot of one-way sensitivity analysis for budget impact comparing high-dose with standard inactivated influenza vaccine strategies



Key: HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; VE – vaccine effectiveness.

Base-case analysis for comparison of high-dose versus adjuvanted inactivated influenza vaccine strategies

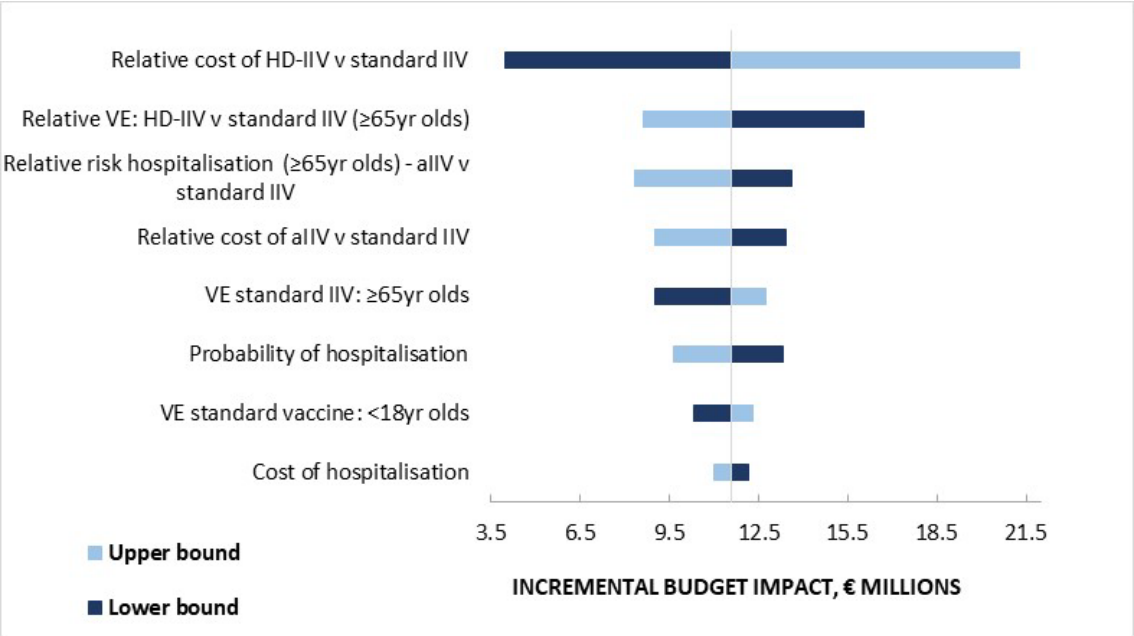
Assuming a vaccine price of €10.99 + VAT for standard IIV and a relative vaccine price of 1.5 times for aIIV (€16.49 + VAT) and 3.25 times for HD-IIV (price of €35.72 + VAT), the one-year incremental budget impact of a HD-IIV strategy, compared with an aIIV strategy, was estimated at €11.6 million (95% CI 2.1 million to 22.0 million). Increased costs associated with procurement of HD-IIV (€15.1 million) were partially offset by cost savings (€3.5 million) from reductions in hospitalisations, GP visits and prescription medication for those with GP visit or medical cards, due to the higher clinical effectiveness of HD-IIV, compared with aIIV, in preventing influenza.

The results of the OWSA demonstrated that the BIA for a strategy based on HD-IIV compared with one based on aIIV was most sensitive to the following parameters:

- relative cost of HD-IIV versus standard IIV
- relative vaccine effectiveness of HD-IIV versus standard IIV in preventing influenza in those aged 65 years and older
- relative risk of hospitalisation with aIIV versus standard IIV in those aged 65 years and older
- relative cost of aIIV versus standard IIV
- vaccine effectiveness of standard IIV in preventing influenza in those aged 65 years and older
- vaccine effectiveness of standard influenza vaccine in preventing influenza in those aged less than 18 years
- probability of hospitalisation for influenza
- cost of hospitalisation.

In the OWSA, the one-year incremental budget impact for a strategy based on HD-IIV (compared with aIIV) across all parameters above ranged from €4.0 million at the lower bound of parameter values for the relative cost of HD-IIV (versus standard IIV) to €21.3 million at the upper bound of the same parameter value (Figure 6.13).

Figure 6.13 Tornado plot of one-way sensitivity analysis for budget impact comparing high-dose with adjuvanted inactivated influenza vaccination strategies



Key: HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; VE – vaccine effectiveness.

Scenario analysis for budget impact of comparison of high-dose versus adjuvanted inactivated influenza vaccine strategies

Given the uncertainty associated with the relative unit cost of aIIV and HD-IIV, versus standard IIV, a scenario analysis was conducted to estimate the effect on the incremental budget impact of a strategy of HD-IIV versus aIIV.

Using the base-case cost of €10.99 plus VAT per dose for standard IIV, the base-case parameter values for the cost per dose of both aIIV and HD-IIV were varied simultaneously. The incremental budget impact of HD-IIV (compared with aIIV) at varying vaccine costs is presented in Table 6.14. The results demonstrate that a strategy of HD-IIV is more costly than aIIV when the difference in the unit cost of the two vaccines is approximately €6.00 or more. However, a strategy of HD-IIV is less costly than aIIV when the difference in the unit costs of the two vaccines is approximately €5.00 or less.

Table 6.14 Incremental budget impact (€, millions) of a high-dose compared with an adjuvanted inactivated influenza vaccine strategy, by unit cost of the vaccines†

		Unit cost of aIIV (€ million) (ex-VAT)							
		10.99	12.00	14.00	16.00	18.00	20.00	22.00	25.00
Unit cost of HD-IIV (€) (ex-VAT)	10.99	-3.98	-4.75	-6.27	-7.79	-9.31	-10.83	-12.35	-14.63
	15.00	-0.94	-1.70	-3.22	-4.74	-6.26	-7.78	-9.30	-11.58
	20.00	2.86	2.09	0.57	-0.94	-2.46	-3.98	-5.50	-7.78
	25.00	6.66	5.89	4.37	2.85	1.33	-0.19	-1.70	-3.99
	30.00	10.46	9.69	8.17	6.65	5.13	3.61	2.09	-0.19
	35.00	14.26	13.49	11.97	10.45	8.93	7.41	5.89	3.61
	40.00	18.06	17.29	15.77	14.25	12.73	11.21	9.69	7.41
	45.00	21.86	21.09	19.57	18.05	16.53	15.01	13.49	11.21

Key: aIIV – adjuvanted inactivated influenza vaccine; HD-IIV – high-dose inactivated influenza vaccine; IIV – inactivated influenza vaccine; VAT – value-added tax.

†Assumes unit cost of €10.99 (ex-VAT) for standard inactivated influenza vaccine.
Indicates aIIV strategy is more costly than HD-IIV strategy.
Indicates HD-IIV strategy is more costly than aIIV strategy.
Closest approximation to the incremental budget impact when the unit costs of aIIV and HD-IIV are set at their base-case values.

Scenario analysis for budget impact of all strategies

Given the uncertainty associated with the cost of all three vaccines, a scenario analysis was also conducted whereby the cost of all three vaccines was varied simultaneously to estimate the strategy with the lowest overall one-year budget impact. The analysis assumed that the unit cost of standard IIV is always lower than the unit cost of aIIV which is always lower than that of HD-IIV. Based on unit costs ranging from €5.00 to €10.99 for standard IIV, €10.99 to €25.00 for aIIV, and €10.99 to €45.00 for HD-IIV, the results suggest that standard IIV would generally have the lowest overall budget impact where the difference in unit cost between standard IIV and aIIV is at least €6.50; otherwise adjuvanted IIV generally would have the lowest overall incremental budget impact. The full set of results is presented in Appendix A6.8.

6.5 Discussion

A de novo dynamic transmission model was developed to characterise the incidence of notified influenza cases in an average influenza season in Ireland in the context of the current HSE Seasonal Influenza Vaccination Programme. The model then assessed the impact of switching to offering vaccination with an enhanced IIV instead of a standard IIV for those aged 65 years and older. The model specifically assessed the use of two enhanced IIVs, aIIV and HD-IIV, given evidence of a statistically significant improvement in one or more clinical outcomes relative to standard IIV.

The epidemiological model output was subsequently used in an economic model to estimate the cost effectiveness and incremental budget impact of using a strategy based on aIIV or HD-IIV for those aged 65 years and older in Ireland. The analysis of cost effectiveness was conducted from both the payer (HSE) and societal perspectives over a single influenza season (six months), while the BIAs estimated the incremental cost to the HSE over one year.

As outlined in Chapter 3, although incidence of influenza is consistently high in those aged 65 years and older, there is considerable variability from year to year in terms of the incidence and the impact on health services, including hospitalisation. The epidemiological model incorporated uncertainty in vaccine effectiveness, so that the outputs reflect the range of incidence observed across multiple seasons.

6.5.1 Main findings

Results from the epidemiological analysis indicated that the estimated number of notified influenza cases in an average influenza season would be 11,845 (95% CI: 7,954 to 15,684). Based on the relative vaccine effectiveness (rVE) of HD-IIV, versus standard IIV, in preventing influenza reported in Chapter 4 (rVE: 24.2%, 95% CI: 9.7 to 36.5%), it was estimated that the use of HD-IIV in those aged 65 years and older would result in an overall reduction of 43.6% (from 11,845 to 6,632 cases) in notified influenza cases across the entire population in a single average influenza season.

In terms of cost effectiveness, both of the aIIV and HD-IIV strategies were more costly and more effective than a strategy using standard IIV. From the payer perspective, a strategy based on aIIV was estimated to dominate the existing strategy based on standard IIV, being less costly and more effective (more QALYs). In 67% of the 10,000 model simulations, the aIIV strategy was less costly and more effective than the existing strategy based on standard IIV and would be deemed cost saving relative to it. It was estimated that a strategy based on HD-IIV was both more costly and more effective than an aIIV-based strategy. The probabilistic ICER for this comparison was estimated at €76,731 per QALY gained, with 73% of the 10,000 model simulations above the WTP threshold of €45,000 per QALY. A strategy based on HD-IIV would therefore be considered not cost effective relative to aIIV. At a WTP threshold of €20,000 per QALY, aIIV had the highest probability of being the cost-effective strategy (65.2%), followed by standard IIV (27.6%). At a WTP threshold of €45,000 per QALY, aIIV again had the highest probability of being the cost-effective strategy (55.4%), followed by HD-IIV (22.9%).

The results of the OWSA highlighted that the ICERs for aIIV relative to standard IIV and HD-IIV relative to aIIV were most sensitive to a number of key parameter

values. For aIIV, these parameters included the relative risk of hospitalisation with aIIV in those aged 65 years and older, the probability of hospitalisation due to influenza, and the relative unit cost of aIIV versus standard IIV. At upper or lower bound values for these three parameters, it was estimated that the ICER for aIIV relative to standard IIV could exceed a WTP threshold of €45,000 per QALY and therefore be considered not cost effective. The ICER for HD-IIV relative to aIIV was most sensitive to parameter values for the relative unit cost of aIIV versus standard IIV, the relative vaccine effectiveness of HD-IIV versus standard IIV in preventing influenza, vaccine effectiveness of standard IIV in those aged 65 years and older, and the relative risk of hospitalisation with aIIV versus standard IIV in those aged 65 years and older. At upper or lower bound values for these four parameters, the ICER for HD-IIV, relative to aIIV, could fall below a WTP threshold of €45,000 per QALY and therefore may be considered cost effective. The results of both one-way sensitivity analysis reflect the wide confidence intervals and therefore high uncertainty associated with these parameter values. Additionally, as noted in Chapter 4, evidence of improved clinical effectiveness of aIIV and HD-IIV for laboratory-confirmed influenza hospitalisations and cases, respectively, are based on single studies. For both vaccines, this is evident in the wide uncertainty for treatment effect, and the impact of that imprecision is reflected in the tornado plots. The limited data available suggests that the point estimates may be a poor proxy for the long-run 'on average' effect. Interpretation of the impact in this case is challenging, because the vaccine prices are also unknown. While prices are subject to negotiation and are ultimately unknown, a more precise estimate of the 'on average' vaccine effectiveness requires large, multi-season studies.

Given the high degree of uncertainty relating to the relative cost of the vaccines, a number of scenario analyses were conducted where the relative costs were varied, both alone and in combination, to understand the impact on the ICERs. When the difference in the cost of a single pre-filled syringe of aIIV and standard IIV was €8 or less, a strategy with aIIV had the largest net monetary benefit at a WTP threshold of €20,000 per QALY. As the difference in vaccine cost exceeded €8 and became increasingly larger, the strategy with the largest net monetary benefit changed from aIIV to standard IIV, with standard IIV generating the largest net monetary benefit when the difference in the cost was €9 or more. However, where the difference in vaccine cost between HD-IIV and aIIV was €9 or less, and the cost of standard IIV was between €5 and €10.99, the HD-IIV strategy generated the largest net monetary benefit. The results demonstrated that the outcome of this CUA is highly sensitive to the relative unit cost of a dose of aIIV and HD-IIV (compared with standard IIV) and this should be a key consideration in any pricing negotiations with vaccine manufacturers.

The probabilistic one-year incremental budget impact of strategies based on aIIV and HD-IIV (versus standard IIV) were -€316,000 (95% CI: -€5.1 million to €3.6 million) and €11.3 million (95% CI: €0.7 million to €22.1 million), respectively. These estimates were also subject to a high degree of uncertainty and the one-way sensitivity analysis highlighted the impact that lower and upper bound parameter values for a number of parameter values, including but not limited to the cost of aIIV and HD-IIV, compared with standard IIV. Similar to the CUA, the scenario analysis highlighted that the BIA results are highly sensitive to changes in the relative cost of the vaccines.

6.5.2 Limitations

The present study is subject to a number of limitations. As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values. In the absence of population level influenza incidence data by age for Ireland, the base-case epidemiological model represents notified influenza cases in an average influenza season. In reality, the incidence of influenza and subsequent incidence of notified influenza cases in any given season can fluctuate greatly. To capture potential fluctuations in incidence of influenza, the base-case model was calibrated based on observed incidence of notified influenza cases from five previous influenza seasons in Ireland (excluding 2020/2021 due to the impact of COVID-19). By limiting the model to notified cases of influenza only, the full disutility and societal cost of influenza are not captured in the analysis. However, notified cases should represent the majority of cases that require medical care and thereby the impact on healthcare resources and quality of life. Furthermore, as the comparator is an existing vaccination strategy, the modelling approach should not have introduced an undue bias for or against the alternative vaccination strategies.

In developing an epidemiological model of influenza infection in Ireland that also captures the current HSE Seasonal Influenza Vaccination Programme which offers a standard IIV, data on the effectiveness of standard IIVs in preventing influenza were required. As no studies on the effectiveness of standard IIV in Ireland were identified, a meta-analysis of estimates from I-MOVE and VEBIS (See Section 4.2.1 for details) was conducted to estimate age-specific vaccine effectiveness. There was variability in the effectiveness, both by season and across countries within season. As the epidemiological model was calibrated based on a hypothetical 'average season', the pooled vaccine effectiveness across a number of seasons is likely to be broadly accurate and was an appropriate estimate to use in the model. The effectiveness of influenza vaccines in preventing influenza varies from season to season and is largely dependent on how well matched the vaccine strains are with the circulating influenza virus strains. Therefore, applying the estimate of vaccine

effectiveness of standard IIV from a meta-analysis, to a model calibrated to estimate incidence of notified influenza in an average influenza season in Ireland, has its limitations. To address this uncertainty, the estimate of standard IIV vaccine effectiveness was varied in both the probabilistic and one-way sensitivity analysis.

To analyse the impact of using HD-IIV, instead of standard IIV, for those aged 65 years and older, the epidemiological model also incorporated the relative vaccine effectiveness of HD-IIV, compared with standard IIV, in preventing influenza in those aged 65 years and over. As outlined in Chapter 4, the relative vaccine effectiveness estimate for this comparison was based on a recently published systematic review.[138] The relative effectiveness estimate was applied to the estimate of standard IIV vaccine effectiveness obtained from our meta-analysis. This created additional uncertainty with regard to the absolute effectiveness of HD-IIV in preventing influenza in those aged 65 years and older. To address this uncertainty, the estimate of relative vaccine effectiveness of HD-IIV was also varied in both the probabilistic and one-way sensitivity analysis.

The evidence from Chapter 4 indicated that HD-IIV was not associated with a statistically significant reduction in influenza-related hospitalisations relative to standard IIV for those aged 65 years and older. However, given that the confidence bounds for the point estimate narrowly crossed the line of no effect, an assumption was made that a reduction in incidence of influenza with HD-IIV would result in a pro-rata reduction in hospitalisations. This was distinct from the approach to aQIV, where incidence of influenza was unchanged, but a reduced likelihood of hospitalisation was applied to cases.

To limit the complexity of the epidemiological model, those aged less than 18 years were modelled as one group. It is noted that the live attenuated influenza vaccine is currently offered to those aged two to 17 years only and therefore the number of vaccinated individuals in the age group less than 18 years old may be slightly overestimated in the model. As the model was calibrated to observed cases of notified influenza, this is unlikely to have impacted the results of the economic analysis.

An important aspect of the epidemiological model was the incorporation of contacts between individuals to simulate the spread of disease. Contacts between individuals were estimated based on the POLYMOD data for the UK.[285] The underlying 2006 study included a number of European countries, but did not include Ireland. Cultural, societal and demographic differences mean that the data may not be fully representative of social interactions in Ireland. However, the age profile of the UK in 2006 is similar to that in Ireland in 2023. Detailed contact matrix data are rare, and the POLYMOD data represent the best available data at present and were used to populate Irish SEIR models during the COVID-19 pandemic.[314] Given that the model

provided an accurate estimate of influenza incidence in the base case scenario, the contact matrix is likely to be sufficiently accurate for application to the Irish population.

The cost of vaccines to the HSE are part of confidential pricing agreements with the vaccine manufacturers, and typically these negotiations commence at the beginning of the procurement process following a decision regarding the eligible cohort for whom the vaccine will be funded. Therefore, for the purpose of this HTA, and in the absence of indicated vaccine prices, a unit cost of €10.99 (ex-VAT) was assumed for standard IIV and relative costs of 1.5 and 3.25 times (versus standard IIV), equating to €16.49 and €35.72, were assumed for aIIV and HD-IIV, respectively. The sensitivity and scenario analysis conducted for both the CUA and BIA highlight the considerable impact that the uncertainty associated with the relative costs of aIIV and HD-IIV had on the results of the economic analysis. In the event that negotiations on the vaccine price of aIIV and HD-IIV are undertaken as part of a competitive tender, careful examination of the analyses presented would be required to identify the potential impact on the cost effectiveness and affordability of the relevant vaccine(s) relating to any deviations in the negotiated prices from those described in the base case scenario.

Given that the epidemiological model represents notified influenza cases in an average influenza season only, and not incidence of all influenza, the relevance of some estimated model parameters should be considered in that context. The age-specific probabilities of infection given contact with an infectious individual were estimated through the epidemiological model calibration process. As the model is limited to notified cases, the differences in these calibrated parameter values may be as a result of varying detection rates for influenza between age groups. Hospitalisation rates were calculated with the number of hospital discharges as the numerator and the number of notified cases in an average influenza season as the denominator. As notified influenza cases are only a subset of all influenza, the estimated hospitalisation rates appear significantly higher than would be expected for all influenza (not limited to notified cases).

The assessment of the safety of enhanced IIVs (Chapter 4) demonstrated that the overall safety profiles of both aIIV and HD-IIV are comparable to that of standard IIV, but that the relative risk of local and systemic reactions with both aIIV and HD-IIV is increased. While the identified safety data were considered broadly applicable to the population aged 65 years and older, there were limited data to support subgroup analysis for this cohort. The increased risk of systemic reactions following vaccination with an enhanced IIV was incorporated into the model, but given the uncertainty associated with the estimates for those aged 65 years and older specifically, the impact on quality of life is potentially underestimated in the model.

However, based on the potential magnitude of differences in the estimates of the relative risk of local and systemic reactions, this is unlikely to impact the overall results of the analysis.

A number of assumptions and parameter values used in the economic model present limitations. An assumption was made that all notified cases of influenza would attend their GP. However, it is acknowledged that this may be an overestimate as some hospitalised cases may have presented directly in the emergency department without first attending the GP. Additionally, national Irish data were not identified to populate a number of parameter values relating to primary care resource use for influenza. Therefore international data on the frequency of GP visits for influenza, the probability of a prescription being issued and the composition of the prescription were used in the analysis. While using international data presents a limitation, the sensitivity analysis suggests that changes to these parameter values would not alter the overall results of the economic evaluation.

The present study considered the cost effectiveness and incremental budget impact of two enhanced IIVs, aIIV and HD-IIV. While the systematic review of clinical effectiveness and safety (Chapter 4) also included cell-based and recombinant IIVs, there were concerns in relation to the applicability of the evidence as the included studies typically did not specifically report estimates for the target population for this HTA, that is, adults aged 65 years and older. Moreover, no evidence of an improvement in clinical outcomes relative to standard IIVs in adults aged 65 years and older was identified for these vaccine types. Given an absence of additional clinical benefit with these vaccine types, an evaluation of the economic impact associated with their use was not undertaken.

6.5.3 Conclusions

Based on the economic evaluation presented, and acknowledging the substantial uncertainty in relation to contracted vaccine prices, the current evidence suggests that switching to a strategy based on an aIIV instead of a standard IIV for those aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme would potentially represent an efficient use of healthcare resources While likely associated with higher vaccine procurement costs, use of aIIV by the programme would potentially be cost-saving (using current list price of €10.99 (ex-VAT) per dose for standard IIV). The outcome of this economic evaluation is highly sensitive to the assumed relative unit cost of the vaccines and as such, replication of simulated costs will be largely dependent on the contracted unit cost of aIIV and HD-IIV, compared with standard IIV. This should be a key consideration in any decision-making and in procurement negotiations with vaccine manufacturers.

7 Organisational issues

Key points

- Ireland has a nationally funded HSE Seasonal Influenza Vaccination Programme which currently funds universal vaccination with a standard inactivated influenza vaccine (IIV) for those aged 65 years and older. It is anticipated that organisational issues for the programme associated with any switch to an enhanced IIV for this cohort would be relatively minor.
- It is expected that there would be no impact on resources related to staff or vaccine storage and handling given that the change would be limited to the vaccine type as opposed to an extension of the immunisation schedule.
- While there is uncertainty in relation to the cost and relative costs of the standard and enhanced IIVs, it is expected that any change to an enhanced IIV would result in an increase in vaccine acquisition costs. This increased cost may be partially or completely offset by a reduction in healthcare utilisation due to a reduction in laboratory-confirmed influenza cases and or influenza-related hospitalisations.
- An information campaign for the public would be an important component of any change to the national immunisation schedule, to educate individuals on the potential risk of complications from influenza, allay any concerns regarding the safety or efficacy of the vaccine and enable informed consent.
- To support such a public awareness communication campaign, consideration would also need to be given to updating the educational material provided to GPs, pharmacists and front-line nursing staff given their important role both in vaccine administration and as a trusted information source for other vaccines given as part of the immunisation programme. While these updates would include information specific to the enhanced IIVs, it is not expected that the updates would result in any additional resource use over that required by existing information campaigns for the influenza programme.
- The Health Protection Surveillance Centre reports annually on vaccination uptake. Vaccination of those aged 65 years and older with an enhanced IIV (instead of a standard IIV) will not result in any changes to the monitoring and evaluation of the influenza programme. It is not known if a switch to an enhanced IIV would lead to change in vaccine uptake.

7.1 Introduction

The aim of this chapter is to provide an overview of the potential organisational issues associated with universal vaccination with an enhanced inactivated influenza vaccine (IIV) in those aged 65 years and older.

7.2 Influenza immunisation schedule in Ireland

Ireland has a nationally funded Health Service Executive (HSE) Seasonal Influenza Vaccination Programme. While anyone can pay for an annual influenza vaccination, for the 2023-2024 influenza season, population groups eligible for (free at the point of delivery) annual influenza vaccination are those:

- aged 65 years and older
- aged 2 to 17 years
- who are a healthcare worker
- who are pregnant
- living in a nursing home or other long-term care facility
- in regular contact with pigs, poultry or waterfowl
- with a health condition that puts them at higher risk of influenza (aged six months and older)
- living with someone who has a health condition that puts them at higher risk of influenza
- who are caring for someone who has a health condition that puts them at higher risk of influenza.[44]

Influenza vaccinations are administered at General Practitioner (GP) surgeries and or community pharmacies; a person can also avail of the vaccine where they live if they reside in a nursing home or are housebound.[23]

The HSE Seasonal Influenza Vaccination Programme is coordinated by the National Immunisation Office (NIO). The HSE established the NIO in 2005 as a coordinating body to standardise the implementation of publicly funded, national immunisation programmes in Ireland.[315] The NIO's responsibilities include:

- collaboration with all stakeholders involved in the delivery and support of immunisation programmes

- development of communication, educational and training materials for the public and health professionals
- management of vaccine supply chains including the procurement, storage and distribution of vaccines
- development and implementation of national standards with regard to aspects of immunisation including protocols, consent forms, education and training and immunisation guidelines for HSE staff.[316]

All immunisation information provided by the NIO is based on the 'Immunisation Guidelines for Ireland' which are developed by the National Immunisation Advisory Committee (NIAC).[315]

7.3 Use of an enhanced inactivated influenza vaccine in those aged 65 years and older

There are two types of influenza vaccines: inactivated influenza vaccines (IIVs) which are administered intramuscularly and intranasal live attenuated influenza vaccine (LAIVs); the latter are used for prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age.[4] Trivalent vaccines (TIVs) are IIVs that contain three strains of influenza virus (two A strains and one B strain), and quadrivalent vaccines (QIVs) are IIVs that contain four strains of influenza virus (two A strains and two B strains).[5]

As outlined in Chapter 2, each year, the WHO issues recommendations to vaccine manufacturers relating to vaccine content and the specific viral subtyping that should be contained within. In the Northern Hemisphere, these recommendations are typically published in February to inform the upcoming influenza season (that is, November the same year to April the following year). These recommendations are based on global surveillance data and are critical to the effectiveness of influenza vaccines.[7] However, due to ongoing evolution of the influenza virus, antigenic mismatch between the virus strains contained in the vaccine and those in circulation can occur. As such, vaccine effectiveness can be suboptimal.[8] Another factor affecting vaccine effectiveness is the individual's immune response, which can be suboptimal due to an ageing or compromised immune system, for example, in older adults (aged 65 years and older) or those with an immunocompromising condition.[9] As such, enhanced influenza vaccines have been developed in an attempt to increase vaccine effectiveness, including:

- adjuvanted IIV (aIIV) – IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response

- high-dose IIV (HD-IIV) – IIV which contains a four-fold increase of HA per strain, (that is, 60µg) instead of 15µg of HA typically included in a standard dose IIV

- vaccines manufactured using alternative substrates to the traditional egg-derived processes, thereby removing the possibility of strain mutation associated with egg-based propagation:[10]

    - cell-based IIV (ccIIV) – IIV manufactured using mammalian cell-culture

    - recombinant HA IV (RIIV) – IIV manufactured using recombinant HA proteins instead of egg-derived processes.[10]

In Ireland, guidance from NIAC states that adjuvanted quadrivalent influenza vaccines (aQIVs) should be used for those aged 65 years and older; standard QIVs are recommended if aQIVs are not available.[11] Currently, only standard QIVs are funded for this age group as part of the HSE Seasonal Influenza Vaccination Programme.[12] As noted in Chapter 2, given the February 2024 recommendations from the WHO on vaccine composition for the 2024-2025 flu season and the related recommendations from the EMA's Emergency Task Force, it is likely that there will be a transition, so that the available authorised IIVs (both standard and enhanced) will be trivalent rather than quadrivalent vaccines.

As highlighted in Chapter 2, indications for the authorised influenza vaccines differ, specifically in relation to age eligibility. While standard IIV may be used in those aged six months and older, use of HD-IIV is limited to those aged 60 years and older while use of aIIV is limited to those aged 65 years and older. Currently the HSE Seasonal Influenza Vaccination Programme offers LAIV to children aged two to 17 years and a standard IIV to adults aged 18 years and older. If a decision is taken to offer an enhanced vaccine to those aged 65 years and older, there is a risk of vaccine errors resulting from the availability of more than one vaccine type for adults. This issue may particularly arise in the context of a July 2024 announcement by the Minister for Health to offer free influenza vaccination through the programme to adults aged 60 years and older for the 2024-2025 influenza season. During the 2021-2022 influenza season, the HSE offered an aIIV to adults aged 65 years and older, while a standard QIV was available to other eligible adult populations. NIO data indicate that 33 influenza vaccination errors were reported from September to November 2021, of which 22 errors related to the incorrect administration of an aIIV (that is, an aIIV was incorrectly given to a person under 65 years (n=13) or a standard QIV was incorrectly given to a person aged 65 years and older (n=9)).[317] While recorded as vaccination errors, the implications of these errors differ. Administration of an aIIV to those aged less than 65 years means that it is being

used outside its licensed indication. Moreover, from a resource perspective, use of an enhanced vaccine in younger immunocompetent age groups may reflect an inefficient use of resources given the higher cost of these vaccines whereas use of a standard IIV in those aged 65 years may mean that they are not adequately protected. If an enhanced influenza vaccine were to be offered to individuals aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme, information materials and any public health information campaign should clearly indicate the vaccine type provided and for whom it is intended. Given increased risk of local and systemic adverse events profiles with a number of the enhanced vaccines, it has been suggested that older adults should continue to be permitted access to a standard IIV should this be their preference; consideration may need to be given as to how this would be captured in administrative data, so such instances are not assumed to be as a result of an error.

In addition, as there is an increased risk of systemic and local adverse events associated with aIIVs and HD-IIVs (although predominantly short-lived and manageable), this risk should be clearly communicated to individuals. Reporting of adverse events is important for all vaccines. Healthcare professionals and vaccine recipients are encouraged to report any harmful effects of vaccination to the Health Products Regulatory Authority.[12]

7.4 Estimated number of eligible adults

Based on projected population figures from the Central Statistics Office, the projected number of adults aged 65 years and older living in Ireland in 2024 is approximately 819,143.[318] There has been a consistent growth in the size of the population aged 65 years and older, with Census 2016 documenting a 19.1% increase relative to Census 2011,[319] and Census 2022 documenting a 21.8% increase in this cohort, relative to Census 2016.[320] Census 2022 data also show that the highest increase in the population was seen among those aged 70 years and older, while the number of people aged 85 years and older has increased by 25%.[321]

7.5 Resources

Use of an enhanced IIV (compared with a standard IIV) for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme will likely have resource implications in terms of the procurement cost of the vaccine. The budget impact analysis (BIA), outlined in Chapter 6, aimed to capture the resource implications over the short term and estimate the incremental costs to the health service associated with such a switch. The BIA also considered the potential costs averted due to associated cost offsets in this cohort.

7.5.1 Staff and resources

Vaccination with an enhanced IIV (compared with a standard IIV) in those aged 65 years and older in Ireland is unlikely to require additional staff as it is limited to a change in the type of vaccine used as opposed to an extension of the immunisation schedule.

According to the results of the economic evaluation reported in Chapter 6, it was estimated that a switch from standard IIVs to HD-IIVs in those aged 65 years and older would result in a reduction of up to 43.6% (95% CI: 23.5% to 59.5%) in notified influenza cases in the total population, over a single average influenza season. This ranged from a reduction of 48.2% (95% CI: 26.5% to 64.9%) in those aged 65 to 69 years, to 53.9% (95% CI: 30.2% to 70.8%) in those aged 75 years and older. Given the estimated reduction in the number of cases, there should be an associated decrease in influenza-related GP consultation rates and hospitalisations, relieving some of the current burden on the health system due to influenza. The one-year incremental budget impact for HD-IIV was estimated at €11.3 million (95% CI: 0.7 million to 22.1 million). The increased vaccine acquisition cost with HD-IIV (€18.9 million) was partially offset by cost savings (€7.6 million) from reductions in hospitalisations, GP visits and prescription medication for those with GP visit or medical cards, due to the higher clinical effectiveness of HD-IIV, compared with a standard IIV, in preventing influenza.

Also based on estimates from the BIA (Chapter 6) a switch from a standard IIV to an aIIV in those aged 65 years and older was considered cost saving, with the one-year incremental budget impact estimated at -€316,000 (95% CI: -5.1 million to 3.6 million). Increased vaccine acquisition costs associated with aIIVs (€3.8 million) was offset by a reduction in hospitalisation costs (€4.1 million) due to the higher clinical effectiveness of aIIV, compared with a standard IIV, in preventing influenza-related hospitalisations. There is substantial uncertainty around these estimates as indicated by the wide confidence intervals as well as the relative risk of hospitalisation. In particular, there is substantial uncertainty in relation to the acquisition costs of the enhanced IIVs, with the results of the evaluation found to be highly sensitive to their costs relative to the standard vaccine. The relative cost of the vaccines was therefore highlighted as a key consideration in any decision-making and in pricing negotiations between the NIO with manufacturers.

As outlined in Chapter 4, HD-IIVs and aIIVs are associated with a statistically significant increase in the risk of a range of local and systemic adverse events relative to standard IIVs. These adverse reactions such as headache, fever or injection site pain following vaccination are typically self-limiting and short-lived. While it is not anticipated that this will result in additional primary care visits, it

cannot be ruled out that some patients may present to the GP for assessment. It must be borne in mind that where the influenza vaccine is administered alongside other vaccines, it may be challenging to determine with which vaccine the adverse events are associated.

7.5.2 Vaccine storage and handling

Vaccines must be transported, stored and maintained within appropriate temperatures and protection from light from the time of manufacture to administration. As with other vaccines currently funded through the HSE Seasonal Influenza Vaccination Programme, enhanced IIVs must be stored and transported between +2°C and +8°C; cold chain procedures must also be followed.[322] The HSE's National Cold Chain Service is responsible for storage and delivery of selected vaccines identified in the Immunisation Schedule. These vaccines are delivered directly to GP surgeries, local HSE offices and community pharmacies following online orders from approved providers, with validated temperature records up to the point of delivery.

The NIO is responsible for managing vaccine procurement and distribution, developing training and communication materials for health professionals and the general public.[316] The National Cold Chain Service stores and delivers vaccines for publicly funded programmes to GP surgeries, hospitals, Local Health Offices and pharmacies with validated temperature records up to the point of delivery. Given that the change proposed is limited to the vaccine type, as opposed to an extension of the immunisation schedule, no additional cost for the cold chain service has been included in the BIA.

Should an enhanced IIV be funded for those aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme, it is important to highlight that standard IIVs would continue to be used for younger cohorts. As such, it is important that procedures are in place at the local level to ensure the correct vaccine type is administered to the correct patient. Additionally, where an enhanced IIV is being funded for those aged 65 and older, updates to the CoVax system would be needed to accommodate this.

7.5.3 Vaccine availability

As outlined in Chapter 2, there are four enhanced IIVs authorised (either centrally by the EMA or nationally by the HPRA) for use in Ireland. However, none are currently marketed in Ireland. If a decision is made to reimburse an enhanced IIV for those aged 65 years and older (as part of the HSE Seasonal Influenza Vaccination Programme), there are a number of processes that need to occur; for example, these vaccines need to be marketed in Ireland and then procured. There is the

potential for vaccine shortages, should international demand exceed available manufacturing capacity. Careful programme planning would be required to manage expectations and minimise any logistical issues.

7.5.4 Information and awareness

Public awareness campaign to support rollout

All information materials for the general public are developed and distributed by the NIO who also manage the national immunisation website www.immunisation.ie.[316]

An information campaign for the public is an important component of any change to the national immunisation schedule, to educate individuals regarding the changes that are being made, allay any concerns regarding the safety or effectiveness of the vaccine and enable informed consent. In the context of changes to the HSE Seasonal Influenza Vaccination Programme, this should include information about differences in the type or frequency of adverse events that may be observed, with this information made available in a manner that it accessible to the eligible population. To support such a public awareness communication campaign, consideration would also need to be given to an educational programme for GPs, pharmacists and front-line nursing staff given their important role both in vaccine administration and as a trusted information source for other vaccines given as part of the immunisation programme. However, in this case, it is not expected that the information campaign would result in any additional resource use than the current information campaign for the influenza programme.

Training

Each vaccinator should be familiar with the Anaphylaxis: Immediate Management in the Community, in the Immunisation Guidelines for Ireland.[323] GP practices should ensure that all general practice clinical staff involved in the provision of vaccination in general practice are aware of all relevant guidelines and should facilitate any training required. Recommended training includes Basic Life Support for Health Care Workers, HSE Immunisation Foundation Programme, and Storing and Managing Vaccines.[324]

The Pharmaceutical Society of Ireland outlines the training that pharmacists must undertake to be permitted to supply and administer vaccines.[325] Along with a standard training programme for vaccination, pharmacists must complete training specific to seasonal influenza; this training is valid for one year. It is assumed that this training is updated each year to reflect the specific influenza vaccines that are available and or being funded. For the 2022-2023 season, uptake of influenza vaccination in those aged 65 years and older was 76.5% (n=568,511). Changing the vaccine type from a standard IIV to an enhanced IIV is unlikely to result in an

increased uptake of the influenza-specific training. Additionally, over 70% of community pharmacies already participate in administering vaccines reimbursed through the HSE programmes, therefore a large proportion of community pharmacists have already completed the core training required for the administration of any vaccine.[326] It is not anticipated that any additional training above what is already required for community pharmacists would be necessary.

7.6 Anticipated vaccine uptake

The historical uptake for seasonal influenza vaccination was obtained from the Health Protection Surveillance Centre (HPSC) and is reported in Chapter 3. From the 2010-2011 season to 2019-2020 (the last season before the onset of the COVID-19 pandemic) the uptake has ranged from 54.5% (2016-2017 season) to 68.5% (2018-2019 season).[327] During the 2020-2021 influenza season, the uptake in those aged 65 years and older increased to 70.5% and it has continued to increase since. For the 2022-2023 influenza season,[115] the influenza vaccination uptake in those aged 65 years and older was 76.5% (n=568,511). Uptake data reflect the administration of influenza vaccines across all settings, that is, GP practices, community pharmacies, long-term care facilities (LTCFs) and hospitals. Beginning in the 2022-2023 season, these data now also capture the vaccination of those working in healthcare settings, so it is possible that some of the increased uptake may reflect better data capture.

Vaccine uptake differs by population and this may have important implications if enhanced IIVs are only reimbursed in specific populations. For example, a decision may be made to only reimburse enhanced IIVs for those living in LTCFs. In a HPSC-Point Prevalence Survey, 162 LTCFs (85 HSE and 77 non-HSE) reported seasonal influenza uptake among residents. For the 2021-2022 season, overall uptake in residents was 93.0% (95.4% in HSE LTCFs). For respite residents, overall uptake was 82.8% (78.7% in HSE LTCFs) for the same season.[328] Alternatively, a decision could be made to only reimburse enhanced IIVs for those aged 75 years and older. In the 2022-2023 season, uptake in those aged 75 years and older was 87.1%.[115]

Uptake figures reported for Ireland are slightly lower than those reported for the UK, for which data suggest that influenza vaccination uptake in those aged 65 years and older was 72.4% (2019-2020 season), 80.9% (2020-2021 season),[329] 82.3% (2021-2022 season)[330] and 79.9% (2022-2023 season).[331] As outlined in Chapter 4 and in Section 7.5.1, there is evidence that both aIIVs and HD-IIVs are associated with improvements in clinical outcomes relative to standard IIVs, with evidence also that they are associated with an increased relative risk of a number of local and systemic adverse events (acknowledging however that these are typically short-lived

and self-limiting). It is not known if these differences in clinical effectiveness and safety would impact on vaccine uptake.

7.6.1 Programme monitoring and evaluation

Since 2012, the HPSC has collated data and reports on the uptake of vaccines provided through the HSE Seasonal Influenza Vaccination Programme.[332] The HPSC reports annually on vaccination uptake. Universal vaccination with an enhanced IIV (instead of a standard IIV) in those aged 65 years and older in Ireland will not result in any changes to the monitoring and evaluation of the influenza programme.

7.7 Discussion

Ireland has a nationally funded HSE Seasonal Influenza Vaccination Programme that currently funds vaccination with a standard IIV for everyone aged 65 years and older. It is anticipated that organisational issues associated with a change to an enhanced IIV would be relatively minor. It is expected that there will be no impact on resources related to staff, vaccine storage and handling or information and awareness. However, it is expected that there would be an increased cost associated with vaccine acquisition. This is captured in the BIA (Chapter 6) along with potential cost offsets associated with any expected reduction in healthcare utilisation arising from a reduction in the notified influenza cases and influenza-related hospitalisations.

An information campaign is an important component of any change to the national immunisation programme. However, it is unlikely that this will result in additional costs over and above those already associated with the current influenza vaccination programme.

8 Ethical, patient and social considerations

Key points

- Seasonal influenza in adults aged 65 years and older is associated with substantial burden both on these individuals and on healthcare services. This burden is in spite of an existing HSE Seasonal Influenza Vaccination Programme which offers a free (at the point of delivery) standard inactivated influenza vaccine (IIV) to this cohort. The proposed change to the existing vaccination programme is limited to a change of vaccine type, that is, to an enhanced IIV.
- The purpose of vaccination is to prevent or reduce the spread and severity of infectious disease. In terms of the benefit-harm balance:
    - evidence of improved outcomes specific to a population aged 65 years and older was available for two of the four enhanced IIVs considered in this HTA. Relative to standard IIVs, there is low-moderate certainty of evidence of a statistically significant reduction in laboratory-confirmed influenza infection and influenza-related hospitalisations with high-dose IIVs (HD-IIVs) and adjuvanted IIVs (aIIVs), respectively.
    - serious adverse events are rare, such that the safety profile of enhanced IIVs is considered acceptable and relatively comparable to that of standard IIVs
    - mild systemic and local reactions are relatively common; an increased risk of systemic and or local adverse reactions were reported with three of the enhanced IIVs considered (aIIVs, HD-IIVs and cell-based IIVs), although it is noted that these are typically transient and self-limiting.
- There is evidence that provision of evidence-based information, knowledge and recommendations from healthcare professionals supports more positive beliefs towards vaccination and a willingness to receive an influenza vaccine.
- Provision of information around the burden of influenza in older adults and the potential for improved protection with the enhanced IIVs will help ensure vaccine decisions are evidence based and may increase an individual's perceived benefit from vaccination. At a population level, improved effectiveness with the enhanced IIVs would benefit community immunity, increasing protection for those who are not vaccinated.
- The healthcare budget is finite and decisions regarding increased spending relating to a change of vaccine could impact the provision of other health technologies within the healthcare system. While there is uncertainty

surrounding the parameter values, evidence from the economic evaluation indicate that use of aIIVs in those aged 65 years and older may represent the most efficient use of healthcare resources. This strategy would be more effective and less costly than the current strategy using standard IIVs although this finding is highly sensitive to the relative cost of these vaccines.

8.1 Introduction

This chapter discusses the ethical issues that should be considered in relation to use of an enhanced inactivated influenza vaccine (IIV) for those aged 65 years and older in the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme. This chapter was broadly developed in line with the structure described in the European network of HTA (EUnetHTA) Core Model.[333] The ethical issues raised around a technology must be assessed in relation to the prevalent patient, social, and moral norms and values relevant to the technology. This section also examines the ethical issues related to the HTA itself. The elements of the EUnetHTA Core Model that were considered relevant to this HTA are described below.

While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent, and, as far as possible, non-coercive. Governments can prevent or reduce the spread of infectious disease through vaccination of the population. Although it is reasonable for a State to aim for high vaccination rates, the balance of benefits and harms to individuals and the wider population must be continuously reviewed. It must also be recognised that individuals have the right to opt out of such immunisation programmes. As a result, there may be conflict between individual and public interests and a balance must be struck between competing values and principles.

In the context of this chapter, the technology under consideration is use of an enhanced IIV instead of a standard IIV for those aged 65 years and older in Ireland. As such, ethical considerations relating to a change in the type of vaccine offered are discussed. Guidance from the National Immunisation Advisory Committee (NIAC) in Ireland states that an adjuvanted quadrivalent influenza vaccine (aQIV) should be used for those aged 65 years and older; a standard QIV is recommended if an aQIV is not available.[11] Currently, only standard QIVs are reimbursed for this age group as part of the HSE Seasonal Influenza Vaccination Programme.[12] As outlined in Chapter 2, World Health Organization (WHO) recommendations to vaccine manufacturers on the composition of influenza vaccines for the 2024-2025 influenza season suggest that these should be trivalent rather than quadrivalent vaccines. This applies to both standard and enhanced vaccines. Recognising that almost all influenza vaccines currently authorised in the European Union are quadrivalent

vaccines, the EMA Emergency Task Force has recommended a gradual transition to trivalent influenza vaccines to ensure vaccine availability. This will likely result in corresponding changes to the NIAC recommendations and to vaccine funding towards trivalent formulations.

8.2 Benefit-harm balance

Seasonal influenza is an acute respiratory infection which places considerable burden on the healthcare system and society in terms of morbidity, mortality, hospitalisations and absenteeism from school and work.[1] The WHO estimates that seasonal influenza can affect up to 20% of the population annually, with severe influenza illness accounting for approximately three to five million cases annually, and up to 650,000 respiratory deaths.[1] A well-matched, annual influenza vaccination may prevent seasonal influenza and the onward transmission of the illness to others. Other preventive measures to compliment annual vaccination include personal measures such as avoiding close contact with infected individuals, respiratory etiquette and good hand hygiene.[334]

As reported in the Epidemiology chapter of this HTA (Chapter 3), data from the Health Protection Surveillance Centre (HPSC) showed that, while overall burden varies from year to year, seasonal influenza in those aged 65 years and older is still associated with a substantial burden on healthcare services despite an existing vaccination programme which offers free (at the point of delivery) influenza vaccination to all those aged 65 years and older. Furthermore, there is evidence that this burden is disproportional to their share of the total population (with those aged over 65 years accounting for 11.7% of the population in 2011[100] rising to 15.1% in 2022[102]). Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), for the seasons 2010-2011 to 2022-2023 (winter period) those aged 65 years and older accounted for, on average:

- 29% of all notified influenza cases (mean=1,656, range: 134 to 4,581 per annum)
- 38% of laboratory-confirmed influenza-related hospital admissions (mean=797, range: 36 to 2,245 per annum)
- 37% of hospital admissions with an ICU stay (mean=43, range: 5 to 108 per annum)
- 66% of influenza-related deaths (mean=60, range: 9 to 159 per annum; equating to an estimated case-fatality rate of 4% per annum).

It is acknowledged that these data are an underestimate of the total burden as not all those with influenza undergo testing to be formally identified as a case. When

disaggregated by five-year age band, there was also evidence that those aged 65 years and older are not homogenous as rates of notified influenza cases, influenza-related hospital admissions and mortality were seen to increase with age.

Hospital In-Patient Enquiry System (HIPE) data, while again showing variability over time, highlight the disproportionate burden associated with influenza in those aged 65 years and older on the public acute hospital setting. Data showed that between 2010 and 2022 (excluding 2020 and 2021 which are not representative due to the COVID-19 pandemic) those aged 65 years and older accounted for 34% of all discharges and 52% of all bed days related to a primary diagnosis of influenza per annum. The mean annual bed days and mean hospital length of stay (LOS) increased with each increase in five-year age band. The mean annual bed days was 635 days (range: 45 to 1,978) in those aged 65 to 69 years compared with 1,258 days (range: 94 to 4,883) in those aged 85 years and older; the mean LOS ranged from seven days in those aged 65 to 69 years to 12 days in those aged 85 years and older.

The purpose of vaccination is to prevent or reduce the spread and severity of infectious disease. For many immunisation programmes, all or almost all of the target population are offered vaccination in the knowledge that perhaps only a small proportion will benefit. The benefit-harm balance must be considered at both the individual level and at the population level. The decision to be vaccinated is made by individuals, typically from the perspective of what the perceived benefit-harm balance is for them personally. The decision-maker, on the other hand, must consider the benefit-harm balance at the population level. Both perspectives are considered in this chapter. As this HTA is to inform a potential change in the vaccine being offered rather than whether or not vaccination should be offered, the following sections are limited to a consideration of the relative, rather than the absolute, potential for benefit and harm.

8.2.1 Benefits and harms at an individual level

Since the development of the enhanced IIVs, numerous studies have been undertaken to determine the efficacy, effectiveness and safety of these vaccines. The evidence generated by these studies was reviewed in Chapter 4. In this section, the benefit-harm balance is considered from an ethical perspective.

Benefits

The findings of an update to a systematic review of the efficacy, effectiveness and safety of enhanced IIVs in adults aged 18 years and older were summarised in Chapter 4. The review included evidence of the relative vaccine effectiveness (rVE) of enhanced IIVs compared with standard IIVs. For high-dose IIVs (HD-IIVs) and

recombinant HA IIVs (RIIVs), there was moderate certainty of evidence that they may reduce laboratory-confirmed influenza infection in adults, compared with standard IIVs. For MF-59® adjuvanted IIVs (aIIVs) there was moderate certainty of evidence that they may reduce influenza-associated hospitalisations in adults, compared with standard IIVs. The results for MF-59® aIIVs and HD-IIVs were considered applicable to adults aged 65 years and older, whereas the evidence for RIIVs was only significant in those aged 50 to 64 years, and not in those aged 65 years and older; as such, it was not considered applicable to older adults. For cell-based IIVs (ccIIVs), the evidence of effectiveness against laboratory-confirmed influenza and laboratory-confirmed influenza-related hospitalisation was not statistically significant.

The main strategy of immunisation programmes across Europe is to protect individuals at increased risk of influenza infection and severe disease course, notably older adults.[335] As outlined in Chapter 4, there is evidence that the effectiveness of standard IIVs is lower in adults aged 65 years and older compared with younger adults and children. Older adults are considered at an increased risk of severe disease from influenza, compared with younger adults and children. Therefore, enhanced IIVs that can demonstrate higher rVE compared with standard IIVs in older adults represent benefits to the individual in terms of protection against acquiring influenza infection and or severe disease.

Harms

The findings of an update to a systematic review of the safety of enhanced IIVs in adults aged 18 years and older were summarised in Chapter 4. Overall, a large evidence base is available on safety that demonstrates the safety profile of the enhanced IIVs is largely similar to that of the standard IIVs. Serious adverse events (SAEs) are rare with both the standard and enhanced IIVs. While based on low certainty evidence, there was no statistically significant difference in the risk of SAEs with MF-59® aIIVs, HD-IIVs, ccIIVs or RIIVs compared with standard IIVs. Three of the enhanced IIVs (aIIV, HD-IIV and ccIIVs) were associated with a statistically significant increased risk of certain systemic and or local adverse events, such as fever, headache, and pain or swelling at the injection site. These mild local and systemic reactions are relatively common, but are noted to be generally self-limiting and transient in their presentation.

As noted in Chapter 4, a post-marketing survey assessment of the safety of aIIVs and HD-IIVs among adults aged 65 years and older from 2020 found that the rates of medical care seeking behaviour were low and did not differ between the two enhanced vaccine groups, indicating no unexpected burden on the healthcare system due to adverse events associated with influenza vaccines.[212] Additional

post-marketing surveillance reports for HD-IIVs in the US,[213] and aIIVs in Italy,[214] did not reveal any new safety concerns. Continued post-marketing surveillance is important to understand the benefits and risks of enhanced influenza vaccines.

The potential risk of such harms relating to enhanced IIVs need to be considered against the potential for these vaccines to provide increased protection against influenza infection and severe disease. As described in Chapter 3, the substantial burden associated with influenza in those aged 65 years and older in Ireland is in the context of an existing HSE Seasonal Influenza Vaccination Programme that offers a free (at the point of delivery) standard IIV to this cohort, indicating that more effective vaccination strategies may be required. If a decision is taken to change to an enhanced vaccine, clear information in relation to the potential for benefit and harm should be provided to older adults to support informed consent. Consideration would also need to be given to how instances wherein an enhanced IIV is offered as part of the HSE Seasonal Influenza Vaccination Programme, but an older person has a preference to receive a standard IIV can be accommodated.

Perceptions and expectations of influenza vaccination

Resilient immunisation programmes seek to maximise enablers to vaccination and minimise barriers by mitigating misperceptions and ensuring vaccine decisions are evidence-based. As enhanced IIVs become increasingly available, and the evidence-base regarding their use in older adults increases, it is important to consider what impact the continued use of standard IIVs may have on vaccination uptake, given evidence that their effectiveness is lower in older adults. However, it is important to note that these standard IIVs still demonstrate effectiveness in reducing the risk of influenza and its complications in older adults.

A qualitative study from 2007 investigated lay beliefs about influenza and influenza vaccination among adults aged 65 years and older in urban and rural communities in South Wales.[336] Interviewees reported perceptions that they were not at risk from influenza, or from serious consequences following infection. Those who refused vaccination were more likely to believe that influenza vaccination resulted in serious side effects, while those who were vaccinated each of the two previous influenza seasons were more likely to believe that influenza vaccination was effective. Of note, those who refused vaccination reported that they would consider a change of mind if prompted directly by their GP, or if they felt they were more likely to catch influenza.

In 2018, a systematic review reported on behaviour-related factors influencing seasonal influenza vaccination attitudes among older adults.[337] The authors reported that people with self-perceived poorer health status were more likely to be vaccinated, while those with self-perceived good health were more likely to refuse vaccination. Habits such as smoking were associated with vaccination refusal, and

recent medical service use was associated with a higher likelihood to have been vaccinated. Similarly, vaccinated older adults tended to believe they were susceptible to influenza infection, while unvaccinated older adults perceived they had low susceptibility to influenza. The provision of information and knowledge from healthcare professionals was associated with more positive beliefs towards vaccination among individuals, whereas the use of mass media as information sources was associated with negative views towards vaccination. Likewise, recommendation from medical staff and from friends or family were cited as reasons for accepting vaccinations.

8.2.2 Benefits and harms at a population level

Community immunity

Community immunity occurs when circulation of a pathogen is significantly curtailed in a community because most of the people it encounters are immune.[338] Immunity is conferred by immunisation and the more people that are vaccinated, the more those who are not vaccinated are indirectly protected because the high immunisation rate stops the virus transmission.[338, 339] Therefore, the benefit provided by community immunity is the extra-protection provided towards non-immune people who are at high risk of severe disease. The infectiousness of the pathogen and the effectiveness of the vaccine determines the threshold for community immunity for any disease.[339]

When considering what is appropriate vaccination coverage, an important factor is the reproduction number (R_0) of the virus, that is, the average number of secondary cases that a typical case will generate.[340] R_0 values greater than one are associated with outbreaks and epidemics.[337] A systematic review from 2014 estimated that the median R_0 for seasonal influenza in the community setting was 1.28 (IQR: 1.19 to 1.37), based on 24 studies reporting 47 separate seasonal epidemic values for R_0.[340] It is important to note that estimates of R_0 are not constant and may be affected by mitigation strategies used, the influenza season and prevailing strains in circulation, and the population under study.

As described in Chapter 3, vaccination uptake data relating to the administration of influenza vaccines funded through the HSE Seasonal Influenza Vaccination Programme indicate that the average seasonal influenza vaccination uptake since 2010-2011 in those aged 65 years and older was 60.7% (range 54.5 to 76.5). The highest uptake was observed in the 2022-2023 season (76.5%), although this may in part reflect the fact that the data were more complete than in previous years as this was the first year that included data relating to the vaccination of healthcare workers and long-term care facility residents. With the exception of the 2022-2023 season, these uptake figures fall short of the recommendation by the Council of the

European Union for EU Member States to achieve a 75% vaccination coverage rate by the 2014-2015 influenza season in key target groups, such as older adults.[117] However, the Irish vaccination coverage rate is relatively high compared with other European countries. The European Centre for Disease Prevention and Control (ECDC) reported that for seasonal influenza vaccination coverage rates in older adults from the 2018-2019 influenza season to the 2020-2021 season, Ireland ranked among the top countries out of 19 countries that reported data for older adults.[341]

A Spanish study from 2012 estimated the vaccination coverage required to establish community immunity against influenza viruses in various settings, taking into account the reproduction number (R_0) and vaccine effectiveness.[342] The vaccination coverage necessary to establish community immunity increases as the R_0 increases and as vaccine effectiveness decreases. In a completely susceptible population, the estimated required vaccination coverage for an influenza virus with an R_0 of 1.25 and vaccine effectiveness of 30% is approximately 75%. To achieve the same vaccination coverage for a virus with an R_0 of 1.5, the required VE is estimated at approximately 45%. For scenarios that assume a prevalence of protected persons in the community, the required vaccine effectiveness to achieve coverage decreases. The required vaccination coverage to achieve community immunity will also be influenced by the openness of the setting — for example, the general community versus retirement homes or long-term care facilities.

The potential for an increase in influenza vaccine effectiveness through the adoption of newer and or enhanced vaccines could have particular relevance to individuals at increased risk of infection due to living in close or shared environments, such as residential care, retirement homes or long-term care facilities. As described in Chapter 3, a systematic review from 2023 reported a disproportionate influenza burden in adults aged 65 years and older, with underlying medical conditions, living in long-term care facilities.[134] As such, an increase in vaccine effectiveness from the adoption of enhanced influenza vaccines may specifically benefit these populations who are particularly vulnerable to influenza infections.

Vaccination is often used as a mechanism to achieve benefits for the greater good, and many individuals experience a minor burden for the few who will experience a substantial benefit. When considering enhanced influenza vaccines, there is potential for improvements to the effectiveness of the vaccine against influenza infection and associated illness, compared with standard IIVs in older adults. In addition to increasing the direct protection for the vaccinated individual, such an increase in VE would strengthen efforts to achieve community immunity, benefiting those at risk, but who are not vaccinated.

Impact on existing national immunisation programme

The purpose of this HTA is to examine the impact of use of an enhanced IIV in those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme. As vaccination is already offered to this group of adults, with a standard IIV, the proposed change to the existing vaccination programme is limited to a change of vaccine type. There are two ethical issues relevant to the current national immunisation programme: whether the use of enhanced IIVs would compromise the target population's (that is, adults aged 65 years and older) perception of the programme, and secondly if the public's perception of the effectiveness of standard IIVs in other populations could be affected.

As discussed above, people's perceptions towards vaccination can be influenced by the quality and source of information provided to them. If an enhanced IIV replaces the use of standard IIV for adults aged 65 years and older, it is possible that the intended recipients may have questions or concerns as to the reason for the change of vaccine. Factors such as perceived low risk of illness combined with concerns relating to vaccine effectiveness and safety have been reported are barriers to vaccine uptake.[336, 337] If an enhanced IIV is offered to older adults, other groups eligible for vaccination through the HSE Seasonal Influenza Vaccination Programme may question why they are also not being offered an enhanced IIV. Healthcare professionals should ensure the provision of clear communication and evidence-based information to those eligible to receive vaccination, especially to older adults as studies have reported information received by healthcare professionals as influential in this cohort's decision to accept vaccination.[336, 337] It is imperative information is provided in a manner that supports the ethical principles of respect for autonomy and informed consent which are foundational pillars that must be upheld.

As part of the HSE Seasonal Influenza Vaccination Programme, an enhanced IIV was previously funded for those aged 65 years and older for the 2021-2022 season. Therefore, if there is a change from the standard IIV to an enhanced IIV, this may help with how the vaccine is perceived by individuals. As described in Chapter 6, from the payer perspective (that is, the HSE), a strategy based on aIIV was found to be cost saving, that is, less costly and more effective, than one based on standard IIV. A strategy based on HD-IIV was found to be more costly and more effective than both standard IIV and aIIV strategies. However, the HD-IIV strategy was considered not cost effective relative to the aIIV strategy, at a willingness-to-pay threshold of €45,000 per quality-adjusted life year (QALY) gained. These findings indicate that use of aIIVs instead of standard IIVs or HD-IIVs may be the most efficient use of healthcare resources for the population. As described in Chapter 6, the outcome of this economic evaluation is highly sensitive to the relative unit costs of a dose of aIIV and HD-IIV (compared with standard IIV), with vaccine cost

identified as a key consideration in any decision-making and in pricing negotiations with vaccine manufacturers.

Compared with vaccination programmes against other infectious diseases, the impact of a change of vaccine on public perception may not be as significant for the HSE Seasonal Influenza Vaccination Programme. The reason for this is that seasonal influenza strains may evolve and differ from year to year, requiring annual vaccination with amendments to the vaccine composition each year to match them to the expected prevailing influenza virus strains.[335] The resilience of public attitudes towards the seasonal influenza programme may also benefit from reports that the COVID-19 pandemic may have increased people's intention to receive the influenza vaccine.[343]

Wider societal impact and caregiver burden

In the economic evaluation described in Chapter 6, the cost effectiveness of strategies based on aIIV and HD-IIV were also examined from the societal perspective (that is, including wider and indirect costs such as productivity loss due to influenza-related illness). From the societal perspective the results were consistent with those from the payer perspective. Under the assumptions outlined in Chapter 6, a strategy based on aIIVs was found to be cost saving compared with a standard IIV strategy, and compared with a strategy based on HD-IIVs. In addition, as mentioned above, individuals living in relatively close environments (such as residential care, retirement homes or long-term care facilities) may especially benefit from these enhanced influenza vaccines. Improved levels of protection in these populations could also have a positive impact on caregivers and healthcare workers in such settings.

8.3 Justice and equity

As outlined above, currently, the HSE Seasonal Influenza Vaccination Programme offers a standard IIV to all adults aged 65 years and older. The focus of this HTA is a potential change to the programme whereby this cohort would instead be offered an enhanced IIV.

8.3.1 Impact of the technology affecting the distribution of healthcare resources

The technology in question is a change from a standard IIV to an enhanced IIV. In the economic evaluation, described in Chapter 6, two types of enhanced IIVs were considered due to the availability of evidence of improved clinical effectiveness relative to standard IIVs and where this evidence was considered applicable to adults aged 65 years and older (as described in Chapter 4). These two vaccines

were aIIVs and HD-IIVs. The population eligible to receive these vaccines comprises approximately 806,000 adults.[286] It is assumed that an enhanced IIV would not result in changes to the existing organisational aspects of the HSE Seasonal Influenza Vaccination Programme.

As outlined in the economic evaluation described in Chapter 6, a vaccination strategy based on aIIV was found to dominate the current strategy based on a standard IIV, being more effective and less costly. A vaccination strategy with HD-IIV was estimated to be more effective again, but would also cost more with an estimated incremental cost-effectiveness ratio (ICER) of €76,731 per QALY gained. As such, it would be considered not cost effective at a willingness-to-pay threshold of €45,000 per QALY gained. These results were noted to be highly sensitive to the relative unit cost of a dose of aIIV and HD-IIV (compared with standard IIV).

As has been described, a high clinical burden of influenza persists among adults aged 65 years and older, which is in the context of an existing annual vaccination programme against seasonal influenza. As outlined in Chapter 4, vaccine effectiveness may be reduced in older adults due to immunosenescence, while enhanced IIVs aim to improve the effectiveness of vaccination, relative to standard IIVs. Therefore, there is the potential for equity to be increased through the provision of such enhanced IIVs to these older populations, recognising that these cohorts tend not to benefit from standard IIVs to the same extent as the general adult population.

The healthcare budget is finite and decisions regarding increased spending relating to a change of vaccine could impact the provision of other health technologies within the healthcare system. Ethical issues of justice and equity with respect to a fair distribution of benefits and burdens should be considered.

8.4 Ethical consequences of HTA

8.4.1 Choice of outcomes

The effectiveness of influenza vaccination was considered in terms of protection against laboratory-confirmed influenza infection and reductions in influenza-associated hospitalisation. From an economic modelling perspective, the impact of three alternative vaccination strategies for the current HSE Seasonal Influenza Vaccination Programme (that is, vaccination with a standard IIV, an aIIV or a HD-IIV) in adults aged 65 years and older, was summarised by translating disease states into changes in quality of life. By summarising illness into a set of discrete health states, there is a risk that an economic model oversimplifies the experience of ill-health. The use of QALYs to capture health benefits does however enable the

calculation of an ICER that is directly comparable with those estimated in other evaluations and against a reference willingness-to-pay threshold.

8.4.2 Timing of assessment

The evidence identified in Chapter 4 on the effectiveness and safety of influenza vaccination was collected at a specific point in time and the conclusions could change over time as the evidence base underpinning the relative effectiveness and safety of enhanced IIVs in older adults increases. The evidence considered related to an updated systematic review (literature published up to 24 July 2023) which re-assessed the effectiveness and safety of the enhanced IIVs in adults. While new evidence was available in relation to the safety of these vaccines since the primary review (literature published up to 7 February 2020) the evidence base for efficacy and effectiveness had not substantially changed and is considered overall to be limited. It has been highlighted that further studies are needed to allow more substantial conclusions relating to the potential benefits of these vaccines.

Evidence availability

The first clinical trials of an IIV, active against the H1N1 strain of influenza A, were undertaken in the mid-1930s, and subsequently, the first IIV was licensed in the US in 1945. As new influenza strains have continued to emerge, IIVs have continually been developed that are active against an increasing range of influenza strains. The standard IIVs currently offered in Ireland were licensed from 2016 to 2018. The enhanced IIVs were licensed from 2018 to 2020. Chapter 4 summarised the results of a recent updated systematic review of the efficacy, effectiveness and safety of enhanced IIVs in adults aged 18 years and older, which included 17 studies that compared the effectiveness of enhanced IIVs with standard IIVs and 42 studies that reported safety outcomes for enhanced IIVs compared with standard IIVs.

8.4.3 Data sources and economic model assumptions

As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values. From an ethical perspective, the concern would be that the model structure or the limitations of the available data may result in conclusions that may unfairly disadvantage a particular population group.

In the absence of population level influenza incidence data by age for Ireland, the base-case epidemiological model represents notified influenza cases only and therefore excludes suspected cases of influenza that were not laboratory-confirmed and influenza-like illness. By limiting the model to notified cases of influenza only, the full disutility and societal cost of influenza are not captured in the analysis.

However, notified cases should represent the majority of cases that require medical care and thereby the impact on both healthcare resources and quality of life associated with influenza. In this analysis, parameter uncertainty was extensively explored through sensitivity and scenario analyses and the findings are largely robust with the exception of uncertainty over vaccine prices.

8.5 Discussion

This chapter examined the ethical issues that should be considered in relation to influenza vaccination in those aged 65 years and older, specifically concerning the change in the type of vaccine offered, from a standard IIV to an enhanced IIV.

As reported in Chapter 3, seasonal influenza in those aged 65 years and older is associated with a substantial burden on healthcare services, despite an existing vaccination programme which offers free (at the point of delivery) influenza vaccination to adults aged 65 years and older. While there is evidence that this burden is disproportionate to their share of the total population, it is acknowledged that the data that informed this chapter are an underestimate of the total burden of influenza.

The evidence of the effectiveness and safety of vaccination with an enhanced IIV is described in detail in Chapter 4. In summary, the evidence demonstrates low-to-moderate certainty of evidence that aIIVs and HD-IIVs may be effective in reducing influenza infection, or influenza-associated hospitalisation, in adults, compared with standard IIVs. For these enhanced IIVs, the evidence was considered applicable to adults aged 65 years and older, whereas the evidence for RIIVs was only significant in those aged 50 to 64 years, and not in those aged 65 years and older; as such, it was not considered applicable to older adults. For cell-based IIVs (ccIIVs), the evidence of effectiveness against laboratory-confirmed influenza and laboratory-confirmed influenza-related hospitalisation was not statistically significant. The safety profile of enhanced IIVs is considered acceptable and relatively comparable with that of standard IIVs.

At an individual level, the decision to be vaccinated is typically informed by what the perceived benefit-harm balance is to them personally. Importantly, it was reported that individuals who had previously refused vaccination would be more likely to consider vaccination if prompted directly by their GP, or if they felt they were more likely to catch influenza.[336] Similar findings were reported in a 2018 systematic review highlighting the importance of the provision of information and knowledge from healthcare professionals to older adults, with this being associated with more positive beliefs towards vaccination.[337]

Decision-makers must consider the benefit-harm balance at a population level. While these considerations are informed by the evidence base relating to the effectiveness and safety of the vaccine, other considerations include concepts such as community immunity, and the cost effectiveness of the vaccine. When considering enhanced IIVs, there is potential for improvements to the effectiveness of the vaccine against influenza infection and associated illness, compared with standard IIVs in older adults. Consequently, a switch to enhanced IIVs could strengthen efforts to achieve community immunity, benefiting those who are at risk, but are not vaccinated.

Based on population estimates, the population eligible to receive these vaccines comprises approximately 806,000 adults. Under the assumptions described in Chapter 6, a strategy based on aIIV was found to be less costly and more effective, than a standard IIV strategy. A strategy based on HD-IIV was found to be not cost effective, compared with an aIIV strategy, at a willingness-to-pay threshold of €45,000. The healthcare budget is finite and decisions regarding increased spending relating to a change of vaccine could impact the provision of other health technologies within the healthcare system.

9 Discussion

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the most efficient use of resources in the healthcare system. The aim of this HTA was to establish the clinical and economic impact of a switch from using a standard to an enhanced inactivated influenza vaccine (IIV) for those aged 65 years and older in the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme. A robust approach to this assessment was employed: a protocol for the HTA was published,[344] and the assessment was conducted in accordance with national and international HTA guidelines.[294, 333] An Expert Advisory Group (EAG) comprising a broad range of key stakeholders was established to support the assessment.

Seasonal influenza is characterised by respiratory and systemic symptoms including fever, malaise, myalgia, headache, sore throat and nasal congestion. Treatment consists of antipyretics, adequate fluid intake, rest and potentially antiviral therapy. However, certain individuals are at increased risk of severe disease and require hospitalisation for complications associated with influenza.[1] A well-matched annual seasonal influenza vaccination is the most effective preventive measure against the disease. Annual influenza vaccination programmes internationally aim to reduce the burden of seasonal influenza typically through the selective vaccination of those at highest risk of severe disease.[2] In Ireland, those aged 65 years and older are eligible (and encouraged) to receive free (at the point of delivery) annual influenza vaccination through the HSE Seasonal Influenza Vaccination Programme.[92] Despite this, there continues to be high morbidity and mortality associated with influenza in this cohort.

9.1 Description of technology

Guidance from the National Immunisation Advisory Committee (NIAC) in Ireland recommends use of an adjuvanted quadrivalent influenza vaccine (aQIV) for those aged 65 years and older; a standard, egg-based QIV is recommended if an aQIV is not available.[11] Currently, only standard QIVs are funded for this age group as part of the HSE Seasonal Influenza Vaccination Programme.[92] In order to inform a decision as to whether enhanced IIVs (such as an aQIV) should be funded as part of the HSE Seasonal Influenza Vaccination Programme, the Department of Health requested that HIQA complete a HTA of use of an enhanced IIV for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme.

A review of current influenza vaccination policy identified that all EU/EEA countries and the UK recommend influenza vaccination for those aged 65 years and older,

however they differ in the vaccine types that are used and the extent to which they are funded for this population. Considering specifically the use of enhanced IIVs, 10 of the 31 included countries fund an enhanced IIV for some or all of the target population. Six of these specifically fund a HD-QIV, one funds an aQIV, one funds either an aQIV, HD-QIV or ccQIV, one funds an aQIV, RIV4 or ccQIV, and one funds all four enhanced IIVs (aQIV, HD-QIV, RIV4 or ccQIV). Additionally, five countries restrict availability to subgroups of the target population, for example, to those aged 75 years or older, or those living in long-term care facilities. The review of international seasonal influenza programmes provides an informative summary of the policies relating to the current use of enhanced IIVs in those aged 65 years and older and funding of the same in other jurisdictions. However, at the time of writing, sources used to inform the review of international practice had not been updated to reflect policies relating to the 2024-2025 influenza season. Therefore, it is possible that there will be changes to the vaccines funded through these programmes, especially in light of new recommendations from the World Health Organization (WHO) and European Medicines Agency (EMA) Emergency Task Force (ETF) regarding the move from quadrivalent to trivalent formulations.[28] While it is often helpful to look at international practice, the burden of disease associated with influenza varies considerably depending on the country, therefore it is important that a decision to amend the influenza vaccination programme should be based on Irish data.

9.2 Epidemiology and burden of disease

Incidence data were sourced from the Health Protection Surveillance Centre (HPSC) and Hospital In-Patient Enquiry (HIPE). It is noteworthy that both HPSC and HIPE data indicate substantial variability from season-to-season and year-to-year, respectively. For the most recent season (2022-2023 season), for which HPSC data are provisional, the ILI consultation rate was 899.6 per 100,000 (n=331) and notified influenza case rate was 718.5 per 100,000 (n=4,581) in those aged 65 years and older for the winter period. While this gives an indication of the burden of influenza on the healthcare system, it is acknowledged that this is an underestimation of the total burden of influenza in the community setting as it is a subset of those who attend the GP with influenza or ILI. It is worth noting that there is no national dataset in Ireland with reliable estimates of influenza. Additionally, ILI may be a poor proxy for influenza as the proportion of ILI that is influenza varies substantially across studies.[345] In those with laboratory-confirmed influenza, the hospital admission rate was 279.0 per 100,000 (n=1,779), the ICU admission rate was 11.0 per 100,000 (n=70), and the mortality rate was 24.9 per 100,000 (n=159) in those aged 65 years and older for the 2022-2023 season. When considering the spread of notified influenza cases across the total population in Ireland, provisional

HPSC data show that for the 2022-2023 season, 30% of all notified influenza cases, 40% of influenza-related hospital admissions, 38% of influenza-related hospital admissions with an ICU stay, and 89% of influenza-related deaths occurred in those aged 65 years and older.

Considering the total population, HIPE data showed evidence of substantial variability in the annual inpatient burden due to influenza as indicated by the wide range for each of the age bands. Patients aged 65 years and older accounted for 52% of all bed days with the highest mean annual number of bed days observed in this age group. In those aged 65 years and older with a primary diagnosis of influenza, there was a mean of 3,853 bed days per annum. However, in considering the years individually, the total bed days fluctuated between 88 in 2010 to 14,914 in 2018. Similarly, considering discharges that involved a stay in ICU, the mean total annual bed days for this cohort was 290 days, but this fluctuated between 140 in 2014 to 539 in 2019. During the seasons of peak COVID-19 incidence (2020-2021 and 2021-2022) there was very low incidence of influenza, although data for 2022-2023 suggest that incidence is returning to pre-pandemic patterns.

Across the five age bands considered in the primary analysis (65 to 69 years, 70 to 74 years, 75 to 70 years, 80 to 84 years and 85 years and older), HPSC data (for the 2022-2023 season) indicate that the total rates of notified cases, hospitalisations and deaths per 100,000 were highest in those aged 85 years and older. These findings are in accordance with international data. In a systematic review of the burden of influenza in those aged 65 years and older, there was evidence of substantial clinical burden of influenza in this cohort, defined by high rates of hospital admissions, ICU admissions and mortality. These outcomes were reported to worsen with increasing age with those aged 75 years and older at increased risk of influenza-related hospital admissions and influenza-related deaths than those aged 65 to 74 years. There was also some evidence that the risk of influenza-related hospital admission continues to increase with age.[134] When considering the Irish data for older adults, while the rates of notified cases, influenza-related hospitalisations and influenza-related deaths were highest in those aged 85 years and older, the rate of ICU admissions was highest in those aged 75 to 79 years and lowest in those aged 80 to 84 years, although this may represent differing ICU policies;[129] alternatively, it could reflect differences in vaccination uptake.

When considering incidence, it should be noted that sentinel practice data represent approximately 10% of the population, which equates to almost 64,000 people aged 65 years and older. As such, the estimates are based on small numbers of cases within the sample, and therefore subject to uncertainty. For this reason, differences in the incidence of influenza between five-year age groups within the age group 65 years and older should be interpreted with some caution. Additionally, the analysis

does not take into account the fact that influenza can result in secondary infections or complications leading to hospital admissions. Those admissions may occur after the infectious period during which influenza can be diagnosed, leading to an under-estimate of the total burden associated with influenza.

This population (aged 65 years and older) are heterogeneous in terms of their health and healthcare requirements.[134] Multimorbidity (the presence of two or more long-term conditions) is common among adults aged 65 years and older. It is estimated that 65% of those aged 65 to 85 years and 82% of those aged 85 years and older have multimorbidity.[346] This places these individuals at higher risk for several conditions including increased vulnerability to influenza.[134] A limitation of the analysis in this assessment is that outcome data relate to the total population aged 65 years and older and it is not known what proportion of the observed influenza-related morbidity and mortality occurred in those with or without multiple long-term conditions, or who were vaccinated or unvaccinated. However, a decision could be made where enhanced vaccines are only used in those aged 65 years and older who also have at least one condition that puts them at increased risk of severe influenza outcomes; this approach is used in Liechtenstein.[71] There is also variation in the population aged 65 years and older with respect to where they live. While it was not possible to identify the proportion of influenza-related hospital admissions that occurred in those living in long-term care facilities, data from other jurisdictions[347, 348] suggests that those living in long-term care facilities are at increased risk of hospital admission due to influenza complications compared with those living at home in the community. This finding could justify restricting the use of enhanced IIVs to those living in such settings; this approach has been adopted in Belgium,[51] Norway,[77] Portugal[80] and Sweden.[89]

In Ireland, the proportion of the population aged 65 years and older has increased over time and population projections predict that the proportion of the total population aged 65 years and older will reach 17.3% in 2028 and 19.0% in 2033.[130] Moreover, the population group aged 80 years and older 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 within the next 30 years.[131] This will likely have a significant knock-on effect on the healthcare system in terms of the healthcare utilisation associated with influenza and other vaccine-preventable diseases.

There appears to be a trend for increasing incidence of notified cases of influenza from 2010-2011 to 2022-2023 in those aged 65 years and older, with corresponding increases in hospital and ICU admission, and mortality. However, it should be noted that, in a survey of respiratory virus testing capacity and practices in acute hospital settings in Ireland (published in 2023),[132] it was 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). Therefore, if the trend of increasing incidence is an artefact of increased surveillance and testing, then the most recent data are a more accurate reflection of the true burden of influenza. Additionally, the 2023 survey showed that 93% of laboratories reported testing specimens from hospital inpatients and ICU patients,[132] making these the most common source of specimens; only 30% of laboratories tested specimens submitted from primary care practices. By focusing on notified influenza cases and laboratory-confirmed influenza-related hospitalisations and mortality, theoretically, these are the cases that had a definite need for medical care. However, it is acknowledged that the true burden of influenza in primary care is likely much higher than that reported given these differences in testing practices.

During the COVID-19 pandemic, all surveillance systems were disrupted and, following little or no circulation of influenza viruses during the 2020-2021 and 2021-2022 seasons, higher levels of influenza virus circulation and subsequent increased notification of cases, hospitalised cases and ICU cases were observed during the 2022-2023 season in Ireland. This was expected following lack of exposure and immunity during the 2020-2021 and 2021-2022 influenza seasons. Changes to testing (such as, increased use of multiplex polymerase chain reaction testing)[132] and changes to health-seeking and testing behaviour during the 2022-2023 season, should also be considered when comparing with previous seasons.

One factor that influences the effectiveness of an influenza vaccination programme is uptake.[349] For the 2022-2023 season, data show an influenza vaccination coverage rate of 76.5% in those aged 65 years and older (with uptake consistently higher in older age groups).[115] Despite an uptake of almost 77% in this cohort, there is still a substantial burden associated with influenza in those aged 65 years and older in Ireland, albeit acknowledging that there is a lack of disaggregated data by vaccination status. Influenza vaccine effectiveness is highly variable and depends on a number of factors such as an individual's age or health status, virus types and subtypes in circulation, and the degree of matching between the circulating strain and the vaccination content.[350] As such, for some seasons, influenza vaccines may be considered effective in terms of the degree of matching between the circulating strain and the vaccine, but vaccinated individuals may still be at risk due to their age and or health status.

9.3 Clinical effectiveness and safety

A recent systematic review update reported on the effectiveness and safety of four types of enhanced IIVs in adults aged 18 years and older: adjuvanted IIVs (aIIVs), high-dose IIVs (HD-IIVs), cell-based IIVs (ccIIVs), and recombinant HA IIVs

(RIIVs).[138] Based on the identification and availability of evidence specifically relating to adult populations aged 65 years and older, the findings of the updated review concerning aIIVs and HD-IIVs could be considered applicable to adults aged 65 years and older. The applicability of the results relating to ccIIVs and RIIV was less clear, due to the majority of studies including populations of mixed age ranges from 18 years and older with limited subgroup analysis by age.

Compared with standard IIVs, there was no significant difference in the effect of aIIVs on laboratory-confirmed influenza. The relative vaccine effectiveness (rVE) of aIIVs against laboratory-confirmed influenza-related hospitalisation was 59.2% (95% CI: 14.6 to 80.5) based on one non-randomised study of interventions (NRSI) in adults aged 65 years and older (moderate certainty of evidence). While aIIVs had no effect on the incidence of laboratory-confirmed influenza, there was evidence of a significant reduction in laboratory-confirmed influenza-related hospitalisations compared with standard IIVs, indicating that they reduced the number of severe cases. There was little to no difference in serious adverse events (SAEs) compared with standard IIVs, with a relative risk (RR) of 0.95 (95% CI: 0.19 to 4.72), based on three randomised controlled trials (RCTs) in adults aged 65 years and older (low certainty of evidence). However, differences in systemic and local adverse reactions were reported. There was a significant increase in the risk of fever (RR 1.95 (95% CI: 1.35 to 2.80)) and pain at the injection site (RR 1.94 (95% CI: 1.58 to 2.40)) with aIIVs compared with standard IIVs.

For the HD-IIVs, rVE against laboratory confirmed influenza was 24.2% (95% CI: 9.7 to 36.5) based on one RCT limited to adults aged 65 years and older (low certainty of evidence). There was little to no difference in SAEs compared with standard IIVs, with a RR of 1.02 (95% CI: 0.42 to 2.46) based on six RCTs (low certainty of evidence). Three of these RCTs were in adults aged 65 years and older, two in adults aged 60 years and older, and one in adults aged 50 to 64 years. However, differences in systemic and local adverse reactions were reported. There was a significant increase in the risk of headache (RR 1.25, 95% CI: 1.13 to 1.40), fever (RR 1.78, 95% CI: 1.25 to 2.54), pain at injection site (RR 1.52, 95% CI: 1.29 to 1.80) and swelling at injection site (RR 1.85, 95% CI: 1.27 to 2.71) with HD-IIVs compared with standard IIVs. It is also interesting to note that, when considering the risk of events, differences in the risk of headache, fever, pain and swelling were statistically significant for standard IIV recipients across aIIV and HD-IIV studies.

For the ccIIVs and RIIVs, no evidence was identified of a significant difference in the efficacy or effectiveness of these vaccines in a population aged 65 years and older. While evidence of effect was observed for RIIVs in terms of laboratory-confirmed influenza in one RCT in adults aged 50 years and older (moderate certainty of evidence), no difference was noted when disaggregated by age (rVE (total

population): 30% (95% CI: 10 to 47); rVE (65 years and older): 17% (95% CI: -20 to 43)). Given the potential for reduced VE in older adults, it highlights the importance of considering the evidence specific to those aged 65 years and older.

As outlined above and in Chapter 4, the estimates to support improved effectiveness of aIIV and HD-IIV relative to standard IIV with respect to laboratory-confirmed influenza hospitalisations and cases, respectively are based on single studies. Moreover, while representing the best available evidence at this time, in each case, these studies were limited to data collected over two consecutive influenza seasons. This is an important limitation given potential substantial variability in influenza vaccine effectiveness across seasons due to mismatch between the administered vaccines and the circulating strains. As such, point estimates based on a small number of seasons may be a poor proxy for the long-run 'on-average' effect.

9.4 Economic evaluation

In order to establish the most up-to-date evidence relating to the models employed and parameters used for the economic evaluation of influenza vaccination, a rapid review was conducted. The findings of this rapid review were used to inform the development of a de novo economic model to assess the cost effectiveness of vaccination with an enhanced IIV in those aged 65 years and older in Ireland. The rapid review sought to identify economic evaluations of influenza vaccination that have been published since 2020 (to cover the last search date for the most recent systematic review)[219] to July 2023.

Nineteen studies were identified, of which 15 were conducted within EU/EEA countries. Fifteen of the included studies were industry funded, three were conducted using government research funding and one study received EU funding. Seven of 19 economic evaluations included in this review adopted a dual perspective (considering both the healthcare and societal perspective) when assessing the cost effectiveness of an intervention. The primary differences in methodological approach were related to the type of model chosen and whether multiple cohorts were modelled, or whether the modelled population was restricted to individuals aged 65 years and older. Static decision-tree models were the most common model choice across the included studies, though these were often not an appropriate choice given the population being modelled. Dynamic transmission models were also commonly used and can be advantageous when modelling infectious diseases owing to their ability to capture indirect community effects. The majority of the studies conducted their analysis over a short time horizon of one year or less. There was variation in the values of absolute vaccine effectiveness (VE) against influenza used across studies, though greater consistency was observed where rVE values were used, which is most likely due to the lack of high-quality studies conducted in this

area. Notably, all 15 of the industry-funded studies found the manufacturers preferred vaccine to be cost effective, which highlights the potential for sponsorship bias across studies, and must be considered when appraising the economic results.

De novo dynamic transmission and economic models were developed that were populated with data relevant to the population aged 65 years and older in Ireland. The modelling took account of the enhanced IIVs for which there was evidence of a statistically significant effect in those aged 65 years and older. As such the strategies considered in the economic model were limited to a comparison of aIIV and HD-IIV with the existing strategy based on standard IIVs. The results of the de novo dynamic transmission model indicated that the estimated number of notified influenza cases in an average influenza season would be 12,350. Based on the relative vaccine effectiveness (rVE) of a HD-IIV versus a standard IIV, it was estimated that the use of a HD-IIV strategy in those aged 65 years would result in an overall reduction of 43.6% (95% CI: 23.5% to 59.5%) in notified influenza cases in a single average influenza season. In terms of cost effectiveness from the payer perspective, an aIIV strategy was estimated to dominate a standard IIV strategy, being less costly, more effective (more quality-adjusted life years (QALYs)), and therefore could be deemed cost saving relative to a standard IIV strategy. It was estimated that a HD-IIV strategy was both more costly and more effective than an aIIV strategy, but it was not considered to be cost effective relative to an aIIV strategy. At a willingness-to-pay (WTP) threshold of €20,000 per QALY, an aIIV strategy had the highest probability of being cost effective (65.2%), followed by a standard IIV strategy (27.6%). At a WTP threshold of €45,000 per QALY, an aIIV strategy again had the highest probability of being cost effective (55.4%), followed by a HD-IIV strategy (22.9%).

Given the high degree of uncertainty relating to the relative cost of the vaccines, a number of scenario analyses were conducted where the relative costs were varied, both alone and in combination, to understand the impact on the incremental cost-effectiveness ratios (ICERs). These analyses demonstrated that the findings were largely robust with the exception of the uncertainty over vaccine prices. A decision rule was presented in Chapter 6 to allow the strategy providing the largest net monetary benefit to be identified by the NIO once the vaccine costs are known as part of contract negotiations.

The probabilistic one-year incremental budget impact of an aIIV and a HD-IIV (versus a standard IIV) were -€316,000 (95% CI: -5.1 million to 3.6 million) and €11.3 million (95% CI: 0.7 to 22.1 million), respectively. These estimates were also subject to a high degree of uncertainty as indicated by the wide confidence intervals. Similar to the CUA, the scenario analysis highlighted that the BIA results are highly

sensitive to changes in the relative cost of the vaccines with this identified as a key consideration in any decision-making.

As outlined in Chapter 4, the clinical effectiveness estimates of improved vaccine effectiveness for aIIV and HD-IIV with respect to laboratory-confirmed influenza hospitalisations and cases, respectively, are each based on single studies both of which collected data over two consecutive influenza seasons. There is potential therefore that the point estimates for both vaccines may be a poor proxy for the long-run 'on-average' given that effectiveness of influenza vaccines in preventing influenza varies to some degree from season to season and is largely dependent on how well matched the vaccine strains are with the circulating influenza virus strains. Multi-season effectiveness data would give a more accurate and potentially more precise estimate of the true vaccine effectiveness. Therefore, there are limitations to using vaccine effectiveness and relative vaccine effectiveness values for standard IIVs and enhanced IIVs, respectively (from meta-analyses) in a model calibrated to estimate the incidence of notified influenza in an average influenza season in Ireland. However, one-way sensitivity analyses and probabilistic sensitivity analyses were undertaken to address these limitations. Additionally, the economic model assumes the influenza vaccination uptake in this population will remain constant regardless of whether a standard IIV or enhanced IIV is used in the programme. However, it is worth noting that influenza vaccination is voluntary. Given that enhanced IIVs, specifically, HD-IIVs and aIIVs, have been found to be more effective in preventing influenza and influenza-related hospital admissions, respectively, in those aged 65 years and older, more individuals may opt to receive the enhanced vaccine. Conversely, it is also noted that these enhanced vaccines are associated with an increased risk of local and systemic side effects, which may result in some individuals opting not to receive the enhanced vaccine. Either way, the economic model does not account for a possible change in influenza vaccination uptake.

9.5 Organisational issues

Given that the change proposed in this HTA is to change the vaccine type used in the HSE Seasonal Influenza Vaccination Programme, rather than to extend the programme itself, it is anticipated that the organisational issues associated with this change will be relatively minor. It is expected that there will be no impact on resources related to staff or vaccine storage and handling but that there may be an increased vaccine acquisition cost associated with any change to an enhanced IIV. This may be partially offset by a reduced need for healthcare visits associated with influenza. An information campaign for the public would be an important component of any change to the national immunisation schedule, to educate individuals on the

potential risk of complications from influenza, allay any concerns regarding the safety or efficacy of the vaccine and enable informed consent. 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.[107] As such, to support a public awareness communication campaign, consideration would also need to be given to updating the educational material provided to GPs, pharmacists and front-line nursing staff, given their important role in both vaccine administration and as a trusted information source for other vaccines given as part of the immunisation programme. While these updates would include information specific to the enhanced IIVs, it is not expected that the updates would result in any additional resource use over that required by existing information campaigns for the influenza programme. In terms of monitoring and evaluation of the influenza vaccination programme, the HPSC already reports annually on vaccination uptake, including uptake specifically in those aged 65 years and older.[276] Therefore, changing the vaccine used in those aged 65 years and older from a standard IIV to an enhanced IIV will not result in any changes to the monitoring and evaluation of the influenza programme.

Should an enhanced IIV be funded for those aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme, it is important to highlight that standard IIVs would continue to be used for younger cohorts. As such, it is important that procedures are in place at the local level to ensure the correct vaccine type is administered to the correct patient. Similarly, as reported above, given the heterogeneous nature of this population in terms of their health status and living arrangements, a decision could be made to restrict the use of enhanced IIVs to those aged 65 years and older who also have an identified clinical condition that puts them at increased risk of severe influenza outcomes, or use could be restricted to those living in long-term care facilities. Again, it would be important that procedures are in place to ensure the correct vaccine type is administered to the correct patient.

9.6 Ethical, patient and social considerations

The proposed change to the existing vaccination programme is limited to a change of vaccine type, that is, to an enhanced IIV. The purpose of vaccination is to prevent or reduce the spread and severity of infectious disease. In terms of the benefit-harm balance there is low-moderate certainty of evidence that enhanced IIVs may reduce laboratory-confirmed influenza infection or influenza-related hospitalisation in adults, with the evidence from aIIVs and HD-IIVs considered applicable to older adults. While mild local and systemic reactions are relatively common, serious adverse events are rare, such that the safety profile of enhanced IIVs is considered

acceptable and relatively comparable to that of standard IIVs. Seasonal influenza in adults aged 65 years and older is associated with substantial burden on healthcare services, despite an existing vaccination programme which offers free (at the point of delivery) standard IIV to this cohort. Vaccination is voluntary and typically is only systematically offered to selected groups (for example, those at elevated risk of severe disease and older adults). Therefore, programmes often rely on individuals seeking vaccination, knowing it is available and being encouraged to avail of it. The provision of evidence-based information, knowledge and recommendations from healthcare professionals has been reported to be associated with more positive beliefs towards vaccination and willingness to receive an influenza vaccine. For example, in a systematic review of the barriers and attitudes towards influenza vaccine uptake, 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. The authors concluded that strategies to encourage uptake should be directed towards creating a better understanding of vaccines and their value through education.[351]

Consideration of the benefit-harm balance at a population level is informed, in part, by the evidence base relating to the effectiveness and safety of a new technology. In the context of evidence that standard IIVs are less effective in older adults likely due to suboptimal immune response, the potential increased effectiveness of enhanced IIVs against influenza infection and associated illness may increase an individual's perceived benefit from vaccination and, at a population level, benefit community immunity, increasing protection for those who are not vaccinated for some reason. However, another factor to be considered in the benefit-harm balance is the cost effectiveness of a new technology. The healthcare budget is finite and decisions regarding increased spending relating to a change to an enhanced IIV in those aged 65 years and older could impact the provision of other health technologies within the healthcare system. Despite this, a strategy of offering aIIVs to those aged 65 years and older may still represent an efficient use of healthcare resources given evidence that this would result in improved health outcomes (QALY gain) and cost savings, relative to a strategy based on standard IIVs. However, as noted, these results are highly sensitive to the relative unit cost of a dose of aIIV and HD-IIV (compared with standard IIV).

9.7 Conclusions

The findings of this HTA show that those aged 65 years and older are disproportionately affected by influenza, both in terms of morbidity and mortality which results in a substantial burden on healthcare services every winter. This burden is in the context of an existing vaccination programme offering a standard IIV with an uptake of 77% in this age group. Serious adverse events are rare with

both standard and enhanced flu vaccines. Current evidence suggests that while associated with a higher incidence of systemic and local reactions, aIIV and HD-IIV may be more effective than standard IIV in reducing cases of laboratory-confirmed influenza and or influenza-related hospitalisations.

The economic evaluation suggests that switching to a strategy based on aIIV instead of standard IIV for those aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme would be cost saving. While likely associated with higher vaccine procurement costs, use of aIIV by the programme would represent an efficient use of healthcare resources. The results of the economic evaluation demonstrated that the cost effectiveness and budget impact are highly sensitive to the relative unit costs of the vaccines, and should be a key consideration in any decision-making and in procurement negotiations with vaccine manufacturers.

References

1. World Health Organization. Fact sheets - Influenza (Seasonal) [Internet]. WHO; 2023 [updated 2023 January 12; cited 2023 May 03]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)/.
2. European Centre for Disease Prevention and Contol. Protect yourself against flu: Learn more about preventive measures [Internet]. ECDC; 2023 [cited 2023 October 16]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/personal-protective-measures
3. Carrillo-Santisteve P, Ciancio BC, Nicoll A, Lopalco PL. The importance of influenza prevention for public health. Human vaccines & immunotherapeutics. 2012;8(1):89-95.
4. European Medicines Agency. European public assessment report (EPAR): Fluenz Tetra [Internet]. EMA; 2022 [updated 2022 August 01; cited 2023 June 22]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/fluenz-tetra#authorisation-details-section.
5. Machado MAA, Moura CS, Abrahamowicz M, Ward BJ, Pilote L, Bernatsky S. Relative effectiveness of influenza vaccines in elderly persons in the United States, 2012/2013-2017/2018 seasons. NPJ vaccines. 2021;6(1):108.
6. World Health Organisation. Recommendations announced for influenza vaccine composition for the 2024-2025 northern hemisphere influenza season [Internet]. Geneva: WHO; 2024 [updated 2024 February 23; cited 2024 March 19]. Available from: https://www.who.int/news/item/23-02-2024-recommendations-announced-for-influenza-vaccine-composition-for-the-2024-2025-northern-hemisphere-influenza-season.
7. Paules CI, Sullivan SG, Subbarao K, Fauci AS. Chasing Seasonal Influenza - The Need for a Universal Influenza Vaccine. The New England journal of medicine. 2018;378(1):7-9.
8. Tregoning JS, Russell RF, Kinnear E. Adjuvanted influenza vaccines. Human vaccines & immunotherapeutics. 2018;14(3):550-64.
9. Cowling BJ, Perera R, Valkenburg SA, Leung NHL, Iuliano AD, Tam YH, et al. Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(7):1704-14.
10. European Centre for Disease Prevention and Contol. Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines [Internet]. Stockholm: ECDC; 2020 [updated 2020 October 01; cited 2023 August 31]. Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-systematic-review-efficacy-vaccines.
11. Royal College of Physicians of Ireland. National Immunisation Advisory Committee Immunisation Guidelines. Chapter 11. Influenza [Internet]. Ireland: Royal College of Physicians of Ireland. National Immunisation Advisory Committee (NIAC); 2022 [updated 2023 September 23; cited 2023

September 23]. Available from: https://www.rcpi.ie/Healthcare-Leadership/NIAC/Immunisation-Guidelines-for-Ireland.
12. Health Service Executive. Flu vaccine for older people [Internet]. HSE; 2023 [cited 2023 June 22]. Available from: https://www2.hse.ie/conditions/flu/vaccine-older-people/.
13. World Health Organization. Influenza seasonal [Internet]. WHO; 2023 [cited 2023 May 03]. Available from: https://www.who.int/health-topics/influenza-seasonal#tab=tab_1.
14. Killingley B, Nguyen-Van-Tam J. Routes of influenza transmission. Influenza Other Respir Viruses. 2013;7 Suppl 2(Suppl 2):42-51.
15. European Centre for Disease Prevention and Contol. Factsheet about seasonal influenza [Internet]. ECDC; 2022 [updated 2022 April 12; cited 2023 May 03]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/facts/factsheet.
16. Petrova VN, Russell CA. The evolution of seasonal influenza viruses. Nature Reviews Microbiology. 2018;16(1):47-60.
17. Baxter D. Evaluating the case for trivalent or quadrivalent influenza vaccines. Human vaccines & immunotherapeutics. 2016;12(10):2712-7.
18. Vatti A, Monsalve DM, Pacheco Y, Chang C, Anaya JM, Gershwin ME. Original antigenic sin: A comprehensive review. Journal of autoimmunity. 2017;83:12-21.
19. Henry C, Palm AE, Krammer F, Wilson PC. From Original Antigenic Sin to the Universal Influenza Virus Vaccine. Trends in immunology. 2018;39(1):70-9.
20. Dunning J, Thwaites RS, Openshaw PJM. Seasonal and pandemic influenza: 100 years of progress, still much to learn. Mucosal immunology. 2020;13(4):566-73.
21. Uyeki TM, Hui DS, Zambon M, Wentworth DE, Monto AS. Influenza. Lancet (London, England). 2022;400(10353):693-706.
22. Ghebrehewet S, MacPherson P, Ho A. Influenza. BMJ (Clinical research ed). 2016;355:i6258.
23. Health Service Executive. Getting the flu vaccine [Internet]. HSE; 2022 [updated 2022 October 03; cited 2023 June 22]. Available from: https://www2.hse.ie/conditions/flu/getting-the-vaccine/.
24. Stowe J, Tessier E, Zhao H, Guy R, Muller-Pebody B, Zambon M, et al. Interactions between SARS-CoV-2 and influenza, and the impact of coinfection on disease severity: a test-negative design. International journal of epidemiology. 2021;50(4):1124-33.
25. Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. Journal of preventive medicine and hygiene. 2016;57(3):E115-e20.
26. Kim YH, Hong KJ, Kim H, Nam JH. Influenza vaccines: Past, present, and future. Reviews in medical virology. 2022;32(1):e2243.
27. Carrat F, Flahault A. Influenza vaccine: the challenge of antigenic drift. Vaccine. 2007;25(39-40):6852-62.
28. European Medicines Agency. Replacement of quadrivalent seasonal influenza vaccines with trivalent vaccines in the EU [Internet]. Amsterdam: EMA; 2024

[updated 2024 March 18; cited 2024 March 27]. Available from: https://www.ema.europa.eu/en/documents/other/replacement-quadrivalent-seasonal-influenza-vaccines-trivalent-vaccines-eu_en.pdf.
29. Treanor JJ. Influenza Vaccination. New England Journal of Medicine. 2016;375(13):1261-8.
30. Health Service Executive. Influenza FAQ 2023/2024 [Internet]. HSE; 2023 [cited 2023 October 16]. Available from: https://www.hse.ie/eng/health/immunisation/hcpinfo/fluinfo/flufaq/faqs.html.
31. European Medicines Agency. European public assessment report (EPAR): Flucelvax Tetra [Internet]. Amsterdam: EMA; 2023 [cited 2023 July 24]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/flucelvax-tetra.
32. European Medicines Agency. European public assessment report (EPAR): Fluad Tetra [Internet]. Amsterdam: EMA; 2023 [cited 2023 June 29]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/fluad-tetra.
33. European Medicines Agency. European public assessment report (EPAR): Supemtek [Internet]. Amsterdam: EMA; 2023 [updated 2023 July 26; cited 2023 July 26]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/supemtek.
34. Health Products Regulatory Authority. Efluelda, suspension for injection in pre-filled syringe [Internet]. Dublin: HPRA; 2020 [cited 2023 July 26]. Available from: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=PA2131/015/001&t=Efluelda,%20suspension%20for%20injection%20in%20pre-filled%20syringe.
35. European Medicines Agency. Medicines under additional monitoring [Internet]. Amsterdam: EMA; 2024 [cited 2024 May 23]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/medicines-under-additional-monitoring#list-of-medicines-under-additional-monitoring-11026.
36. European Medicines Agency. List of medicines under additional monitoring [Internet]. Amsterdam: EMA; 2024 [updated 2024 April 22; cited 2024 May 23]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/medicines-under-additional-monitoring/list-medicines-under-additional-monitoring
37. European Medicines Agency. Additional monitoring factsheet [Internet]. Amsterdam: EMA; 2024 [cited 2024 May 23]. Available from: https://www.ema.europa.eu/en/documents/other/what-does-black-triangle-mean_en.pdf.
38. World Health Organization. Coadministration of seasonal inactivated influenza and COVID-19 vaccines. Interim guidance [Internet]. WHO; 2021 [updated 2021 October 21; cited 2023 June 21]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-coadministration-influenza-vaccines.
39. Joint Committee on Vaccinnation and Immunisation. JCVI Minute of the meeting held on 07 February 2024 (Draft) [Internet]. London: JCVI; 2024

[updated 2024 March 21; cited 2024 April 05]. Available from: https://app.box.com/s/iddfb4ppwkmtjusir2tc.
40. Athan E, Baber J, Quan K, Scott RJ, Jaques A, Jiang Q, et al. Safety and Immunogenicity of Bivalent RSVpreF Vaccine Coadministered With Seasonal Inactivated Influenza Vaccine in Older Adults. Clinical Infectious Diseases. 2023.
41. Health Products Regulatory Authority. Fluarix Tetra suspension for injection in pre-filled syringe Influenza vaccine (split virion, inactivated) [Internet]. Dublin: HPRA; 2018 [cited 2023 September 20]. Available from: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=PA1077/134/001&t=Fluarix%20Tetra%20suspension%20for%20injection%20in%20pre-filled%20syringe%20Influenza%20vaccine%20(split%20virion,%20inactivated).
42. Health Products Regulatory Authority. Quadrivalent Influenza Vaccine (split virion, inactivated), suspension for injection in pre-filled syringe Quadrivalent influenza vaccine (split virion, inactivated) [Internet]. Dublin: HPRA; 2016 [cited 2023 September 20]. Available from: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=PA2131/013/001&t=Quadrivalent%20Influenza%20Vaccine%20(split%20virion,%20inactivated),%20suspension%20for%20injection%20in%20pre-filled%20syringe%20Quadrivalent%20influenza%20vaccine%20(split%20virion,%20inactivated).
43. Health Products Regulatory Authority. Influvac Tetra, suspension for injection in pre-filled syringe (influenza vaccine, surface antigen, inactivated) [Internet]. Dublin: HPRA; 2017 [cited 2023 September 20]. Available from: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=PA2010/053/002&t=Influvac%20Tetra,%20suspension%20for%20injection%20in%20pre-filled%20syringe%20(influenza%20vaccine,%20surface%20antigen,%20inactivated).
44. Health Service Executive. Flu vaccine overview [Internet]. HSE; 2023 [cited 2023 July 24]. Available from: https://www2.hse.ie/conditions/flu/vaccine/.
45. European Vaccination Information Portal. Vaccination schedules in the EU/EEA [Internet]. ECDC; 2023 [updated 2020 March 13; cited 2023 July 24]. Available from: https://vaccination-info.eu/en/vaccination/when-vaccinate/vaccination-schedules-eueea.
46. European Centre for Disease Prevention and Control. Vaccine Scheduler. Influenza: Recommended vaccinations [Internet]. ECDC; 2023 [updated 2024 January 31; cited 2024 April 08]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=15&SelectedCountryIdByDisease=-1.
47. UK Health Security Agency. National flu immunisation programme 2024 to 2025 letter [Internet]. London: UKHSA; 2024 [updated 2024 March 12; cited 2024 March 12]. Available from: https://www.gov.uk/government/publications/national-flu-immunisation-

programme-plan-2024-to-2025/national-flu-immunisation-programme-2024-to-2025-letter.
48. Federal Ministry of Social Affairs, Health, Care and Consumer Protection (Austria). Vaccination Plan Austria [Internet]. Vienna: Federal Ministry of Social Affairs, Health, Care and Consumer Protection; 2024 [updated 2024 January 08; cited 2024 April 08]. Available from: https://www.sozialministerium.at/Themen/Gesundheit/Impfen/Impfplan-%C3%96sterreich.html.
49. Federal Ministry of Social Affairs, Health, Care and Consumer Protection (Austria). Influenza. Questions and answers for citizens [Internet]. Vienna: Federal Ministry of Social Affairs, Health, Care and Consumer Protection; 2023 [cited 2023 October 24]. Available from: https://impfen.gv.at/impfungen/influenza/fragen-und-antworten-fur-burger-innen.
50. Federal Ministry of Social Affairs, Health, Care and Consumer Protection (Austria). Influenza. Questions for Retirement and Nursing Homes (APH) [Internet]. VIenna: Federal Ministry of Social Affairs, Health, Care and Consumer Protection; 2023 [cited 2023 October 24]. Available from: https://impfen.gv.at/impfungen/influenza/fragen-fur-alten-und-pflegeheimen-aph.
51. Conseil Supérieur de la Santé (Belgium). Vaccination against seasonal flu. Winter season 2023-2024 [Internet]. Brussels: CSS; 2023 [updated 2023 September 27; cited 2023 October 24]. Available from: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20230927_css-9767_grippe_saison_23-24_vweb.pdf.
52. National Institute for Health and Disability Insurance (Belgium). Reimbursement of the seasonal flu vaccine [Internet]. Brussels: NIHDI; 2023 [updated 2023 October 12; cited 2023 October 24]. Available from: https://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/remboursement/Pages/remboursement-vaccin-grippe-saisonniere.aspx.
53. Croatian Institute of Public Health. Influenza vaccination for people at increased risk of developing a severe form of influenza and its complications [Internet]. Zagreb: HZJZ; 2023 [updated 2023 November 28; cited 2024 April 04]. Available from: https://www.hzjz.hr/sluzba-epidemiologija-zaraznе-bolesti/cijepljenje-protiv-gripe-za-osobe-s-povecanim-rizikom-od-razvoja-teskog-oblika-gripe-i-njezinih-komplikacija/.
54. European Centre for Disease Prevention and Contol. Vaccine Scheduler. Cyprus: Recommended vaccinations [Internet] [Internet]. Europe: ECDC; 2023 [updated 2023 April 24; cited 2023 October 24]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByCountry?SelectedCountryId=46&IncludeChildAgeGroup=false&IncludeAdultAgeGroup=true&IncludeAdultAgeGroup=false.
55. Statens Serum Institut (Denmark). Influenza vaccination [Internet]. Copenhagen: SSI; 2023 [updated 2023 November 03; cited 2024 April 04]. Available from: https://www.ssi.dk/vaccinationer/influenzavaccination.

56. Statens Serum Institut (Denmark). Fluzone High Dose Quadrivalent 4-valent vaccine [Internet]. Copenhagen: SSI; 2023 [updated 2023 September 11; cited 2023 October 24]. Available from: https://www.ssi.dk/vaccinationer/vaccineleksikon/i/influenzavaccine-4-valent-hojdosis.
57. The Danish Health Authority. For you who need to be vaccinated against influenza and covid-19 [Internet]. Copenhagen: SST; 2023 [updated 2023 September; cited 2023 October 24]. Available from: https://www.sst.dk/-/media/Udgivelser/2023/Vaccination/Efteraar/2Vaccination_Pjece_23---Efteraarets-vaccinationsprogram-mod-influenza-og-covid-19_FINAL.ashx.
58. Estonian Health Insurance Fund (Tervisekassa). News: In mid-October, at-risk groups will receive a free flu vaccine [Internet]. Tallinn: Estonian Health Insurance Fund (Tervisekassa); 2023 [updated 2023 September 29; cited 2023 October 24]. Available from: https://vaktsineeri.ee/et/uudised/oktoobri-keskel-saavad-riskiruhmad-tasuta-gripivaktsiini.
59. Finnish Institute for Health and Welfare. Influenza vaccine [Internet]. Helsinki: THL; 2024 [updated 2024 January 01; cited 2024 April 08]. Available from: https://thl.fi/en/topics/infectious-diseases-and-vaccinations/vaccines-a-to-z/influenza-vaccine.
60. Ministry of Health and Prevention (France). Vaccination schedule [Internet]. Paris: Ministry of Health and Prevention; 2023 [updated 2023 September 20; cited 2023 October 24]. Available from: https://sante.gouv.fr/prevention-en-sante/preserver-sa-sante/vaccination/calendrier-vaccinal.
61. Robert Koch Institute (Germany). Answers to frequently asked questions about vaccination against influenza [Internet]. Berlin: RKI; 2023 [updated 2023 September 18; cited 2023 October 24]. Available from: https://www.rki.de/SharedDocs/FAQ/Impfen/Influenza/FAQ_Uebersicht.html.
62. Robert Koch Institute (Germany). Epidemiological Bulletin. Recommendations of the Standing Vaccination Commission at the Robert Koch Institute 2024 [Internet]. Berlin: RKI; 2024 [updated 2024 January 25; cited 2024 April 08]. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2024/Ausgaben/04_24.pdf?__blob=publicationFile.
63. Robert Koch Institute (Germany). Recommendations of the Standing Committee on Vaccination (STIKO). Immunisation Schedule [Internet]. Berlin: RKI; 2023 [updated 2023; cited 2023 October 24]. Available from: https://www.rki.de/DE/Content/Infekt/Impfen/Materialien/Downloads-Impfkalender/Impfkalender_Englisch.pdf?__blob=publicationFile.
64. Ministry of Health (Greece). National Adult Vaccination Program 2023 [Internet]. Athens: Ministry of Health; 2023 [updated 2023 February 24; cited 2023 October 24]. Available from: https://www.moh.gov.gr/articles/health/dieythynsh-dhmosias-ygieinhs/emboliasmoi/ethniko-programma-emboliasmwn-epe-enhlikwn/11251-ethniko-programma-emboliasmwn-enhlikwn-2023.
65. Directorate of Health (Iceland). Overview of general vaccinations in Iceland Reykjavik: Directorate of Health; 2023 [updated 2023 June; cited 2023 October 24]. Available from:

https://assets.ctfassets.net/8k0h54kbe6bj/403Tf05stb5BdJndgSVqG2/65dbe748b42aa396e388ab80b884acee/Yfirlit_yfir_almennar_b__lusetningar_____slandi_2023_EN_KSJ.pdf.
66. Heilsuvera (Iceland). Influenza [Internet]. Reykjavik: Capital Region Health Care and the Directorate of Health; 2023 [updated 2023 May 05; cited 2023 October 24]. Available from: https://www.heilsuvera.is/markhopar/sjukdomar-fravik-einkenni/influensa/.
67. Ministry of Health (Italy). Vaccination schedule [Internet]. Rome: Ministry of Health; 2023 [updated 2023 August 09; cited 2023 October 24]. Available from: https://www.salute.gov.it/portale/vaccinazioni/dettaglioContenutiVaccinazioni.jsp?lingua=italiano&id=4829&area=vaccinazioni&menu=vuoto.
68. Ministry of Health (Italy). Flu prevention and control: recommendations for the 2023-2024 season [Internet]. Rome: Ministry of Health; 2023 [cited 2023 Octboer 24]. Available from: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2023&codLeg=93294&parte=1%20&serie=null.
69. Disease Prevention and Control Latvia (SPKC). Recommended vaccination and the most suitable vaccines. For adults [Internet]. Riga: Disease Prevention and Control (SPKC); [cited 2023 October 24]. Available from: https://www.vm.gov.lv/lv/media/11925/download?attachment.
70. Disease Prevention and Control Latvia (SPKC). Information and advice to citizens on influenza prevention measures [Internet]. Riga: Disease Prevention and Control (SPKC); 2023 [updated 2023 October 12; cited 2023 October 24]. Available from: https://www.spkc.gov.lv/lv/informacija-un-ieteikumi-iedzivotajiem-par-gripas-profilakses-pasakumiem.
71. Federal Office of Public Health (Switzerland). Information about the flu vaccines [Internet]. Bern: FOPH; 2024 [updated 2024 March; cited 2024 April 04]. Available from: https://impfengegengrippe.ch/de-ch/impfung/impfstoffe.html.
72. European Centre for Disease Prevention and Contol. Vaccine Scheduler. Lithuania: Recommended vaccinations [Internet]. ECDC; 2023 [updated 2022 September 30; cited 2023 October 24]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByCountry?SelectedCountryId=120&IncludeChildAgeGroup=false&IncludeAdultAgeGroup=true&IncludeAdultAgeGroup=false.
73. Ministry of Health (Luxembourg). Protect yourself with vaccination [Internet]. Luxembourg: Ministry of Health; 2024 [updated 2024 January 10; cited 2024 April 05]. Available from: https://sante.public.lu/fr/espace-citoyen/dossiers-thematiques/g/grippe-saisonniere/vaccination-grippe.html.
74. European Centre for Disease Prevention and Contol. Vaccine Scheduler. Malta: Recommended vaccinations [Internet]. Europe: ECDC; 2023 [updated 2023 April 13; cited 2023 October 24]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByCountry?SelectedCountryId=130&IncludeChildAgeGroup=false&IncludeAdultAgeGroup=true&IncludeAdultAgeGroup=false.
75. National Institute for Public Health and the Environment (RIVM). Where and

when to get the flu vaccine [Internet]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2023 [updated 2022 December 15; cited 2023 October 24]. Available from: https://www.rivm.nl/en/flu-and-flu-vaccine/where-and-when-to-get-the-flu-vaccine.

76. National Institute for Public Health and the Environment (RIVM). Flu vaccine [Internet]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2022 [updated 2022 December 15; cited 2023 October 24]. Available from: https://www.rivm.nl/en/flu-and-flu-vaccine/vaccine.
77. Norwegian Institute of Public Health. Vaccine recommendations for influenza season 2023-2024 [Internet]. Oslo: NIPH; 2024 [updated 2024 February 23; cited 2024 April 05]. Available from: https://www.fhi.no/en/va/influenza-vaccine/about-seasonal-influenza-vaccine/.
78. National Institute for Public Health (Norway). Influenza vaccine for risk groups [Internet]. Oslo: NIPH; 2023 [updated 2023 August 28 cited 2023 October 24]. Available from: https://www.fhi.no/en/va/influenza-vaccine/influenza-vaccine-for-risk-groups2/.
79. National Institute of Public Health-National Institute of Hygiene (Poland). Flu vaccine [Internet]. Warsaw: National Institute of Public Health - NIH; 2024 [updated 2024 March 14; cited 2024 April 05]. Available from: https://szczepienia.pzh.gov.pl/szczepionki/grypa/?strona=9#jak-wyglada-refundacja-szczepionek-przeciw-grypie-w-sezonie-2023/2024.
80. Ministry of Health (Portugal). Flu and Covid-19 vaccination [Internet]. Lisbon: SNS: Government of the Portugese Republic -Ministry of Health; 2023 [updated 2024 January 15; cited 2024 April 05]. Available from: https://www.sns24.gov.pt/tema/vacinas/vacinacao-gripe-e-covid-19/.
81. Directorate General for Health (Portugal). Seasonal Flu Vaccination Campaign: Autumn-Winter 2023-2024; Rule nº 006/2023 of 26/09/2023 [Internet]. Lisbon: Directorate General for Health; 2023 [updated 2023 September 26; cited 2024 April 10]. Available from: https://www.dgs.pt/ficheiros-de-upload-2013/norma-para-vacinacao-sazonal-contra-a-gripe-2023-pdf.aspx
82. Regina Maria Private Health Network (Romania). Be stronger than the flu. Get vaccinated against the flu now [Internet]. Romania: Regina Maria Private Health Network; 2023 [cited 2023 October 24]. Available from: https://www.reginamaria.ro/gripa.
83. Public Health England. Surveillance of influenza and other respiratory viruses in the UK: Winter 2017 to 2018 [Internet]. UK: PHE; 2018 [updated 2018 May; cited 2023 September 01]. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20220401215804/https:/www.gov.uk/government/statistics/annual-flu-reports.
84. National Institute of Public Health of the Republic of Slovenia (NIJZ). Instructions and recommendations for vaccination [Internet]. Ljubljana: NIJZ; 2024 [updated 2024 March 07; cited 2024 April 05]. Available from: https://nijz.si/nalezljive-bolezni/cepljenje/navodila-in-priporocila-za-cepljenje/.
85. Ministry of Health (Spain). Seasonal vaccination recommendations update 2023-2024 [Internet]. Madrid: Ministry of Health; 2023 [cited 2023 October 24]. Available from: https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/progr

amasDeVacunacion/docs/Recomendaciones_vacunacion_gripe.pdf.
86. Ministry of Health (Spain). Immunizations and Immunization Program. Lifetime Vaccination Schedule 2023 [Internet]. Madrid: Ministry of Health; 2023 [cited 2023 October 24]. Available from: https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/calendario-y-coberturas/home.htm.
87. Ministry of Health (Spain). Immunizations and Immunization program. Technical Documents [Internet]. Madrid: Ministry of Health; 2023 [cited 2023 October 24]. Available from: https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/comoTrabajamos/documentos-tecnicos.htm.
88. Ministry of Health (Spain). Immunizations and Immunization program. Questions and Answers [Internet]. Madrid: Ministry of Health; 2023 [cited 2023 October 24]. Available from: https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/programasDeVacunacion/faq/home.htm.
89. Public Health Agency of Sweden (Fohm). Recommendations about flu vaccination to at risk groups. Version 8, August 2023 [Internet]. Solna: Public Health Agency of Sweden (Fohm),; 2023 [updated 2023 August; cited 2023 October 24]. Available from: https://www.folkhalsomyndigheten.se/contentassets/af9f68e3cb324aaf818f8e7d53132090/rekommendationer-influensavaccination-riskgrupper.pdf.
90. UK Health Security Agency. Guidance. National flu immunisation programme 2024 to 2025 letter [Internet] [Internet]. London: UKHSA; 2024 [updated 2024 March 12; cited 2024 April 10]. Available from: https://www.gov.uk/government/publications/national-flu-immunisation-programme-plan-2024-to-2025/national-flu-immunisation-programme-2024-to-2025-letter.
91. UK Health Security Agency. Guidance. Flu vaccines for the 2023 to 2024 season [Internet]. UK: UKHSA; 2023 [updated 2023 August 08; cited 2023 October 24]. Available from: https://www.gov.uk/government/publications/flu-vaccines-for-the-current-season/flu-vaccines-for-the-2023-to-2024-season.
92. Health Service Executive. Seasonal Influenza Vaccination Programme 2023/2024 [Internet]. Dublin: HSE; 2023 [updated 2024 January 26; cited 2024 March 19]. Available from: https://www.hse.ie/eng/health/immunisation/hcpinfo/fluinfo/fluhp.html.
93. Centers for Disease Control and Prevention. Influenza (Flu) - How Flu Spreads [Internet]. CDC; 2022 [updated 2022 September 20; cited 2023 May 03]. Available from: https://www.cdc.gov/flu/about/disease/spread.htm#:~:text=However%2C%20infants%20and%20people%20with,infect%20a%20person%27s%20respiratory%20tract.
94. Alonso WJ, Yu C, Viboud C, Richard SA, Schuck-Paim C, Simonsen L, et al. A global map of hemispheric influenza vaccine recommendations based on local patterns of viral circulation. Scientific Reports. 2015;5(1):17214.
95. Chong KC, Lee TC, Bialasiewicz S, Chen J, Smith DW, Choy WSC, et al.

Association between meteorological variations and activities of influenza A and B across different climate zones: a multi-region modelling analysis across the globe. Journal of Infection. 2020;80(1):84-98.
96. Health Protection Surveillance Centre. Influenza Surveillance Reports [Internet]. Dublin: HPSC; 2023 [cited 2023 May 03]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/surveillance/influenzasurveillancereports/.
97. Health Protection Surveillance Centre. Sentinel GP surveillance of clinical diseases [Internet]. Dublin: HPSC; 2012 [updated 2012 October 26; cited 2023 May 03]. Available from: https://www.hpsc.ie/a-z/other/syndromicsurveillance/sentinelgpsurveillance/.
98. European Centre for Disease Prevention and Contol. TESSY - The European Surveillance System - Influenza Reporting Protocol 2022 [Internet]. Europe: ECDC; 2022 [updated 2022 October; cited 2023 May 03]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Influenza-Reporting-Protocol_Oct2022.pdf.
99. Healthcare Pricing Office. Hospital In-patient enquiry (HIPE) Data dictionary 2022, Version 14.0 [Internet]. Dublin: HPO; 2022 [updated 2022; cited 2023 October 31]. Available from: http://hpo.ie/hipe/hipe_data_dictionary/HIPE_Data_Dictionary_2022_V14.0.pdf.
100. Central Statistics Office. Census 2011 Reports [Internet]. Cork: CSO; 2023 [cited 2023 November 14]. Available from: https://www.cso.ie/en/census/census2011reports/.
101. Central Statistics Office. Census 2016 Reports [Internet]. Cork: CSO; 2023 [cited 2023 November 14]. Available from: https://www.cso.ie/en/census/census2016reports/.
102. Central Statistics Office. Census of Population 2022 [Internet]. Cork: CSO; 2023 [cited 2023 November 17]. Available from: https://www.cso.ie/en/statistics/population/censusofpopulation2022/.
103. Public Health England. National flu immunisation programme 2021 to 2022 letter [Internet]. PHE; 2021 [updated 2021 July 28; cited 2023 May 03]. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20220412180617/https:/www.gov.uk/government/publications/national-flu-immunisation-programme-plan/national-flu-immunisation-programme-2021-to-2022-letter.
104. European Centre for Disease Prevention and Contol. Seasonal influenza - Annual Epidemiological Report for 2021-2022 [Internet]. 2022 [updated 2022 December 15; cited 2024 February 28]. Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-annual-epidemiological-report-2021-2022.
105. European Centre for Disease Prevention and Contol. Seasonal influenza - Annual Epidemiological Report for 2022/2023 [Internet]. Europe: ECDC; 2023 [updated 2023 July 27; cited 2023 September 01]. Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-annual-epidemiological-report-20222023.

106. Central Statistics Office. Older Persons Information Hub. Population aged 65+ [Internet]. Cork: CSO; 2023 [updated 2023 November 20; cited 2024 March 28]. Available from: https://www.cso.ie/en/releasesandpublications/hubs/p-opi/olderpersonsinformationhub/ageingpopulation/populationaged65/.
107. World Health Organization. Readiness for influenza during the COVID-19 pandemic [Internet]. 2020 [updated 2020 November 06; cited 2023 May 03]. Available from: https://iris.who.int/bitstream/handle/10665/336438/WHO-2019-nCoV-Influenza_readiness_COVID-19-2020.1-eng.pdf?isAllowed=y&sequence=1.
108. EuroMOMO. EuroMOMO Bulletin, Week 12, 2024. EuroMOMO pooled estimates show normal levels of excess mortality [Internet]. Copenhagen: EuroMOMO; 2024 [updated 2024; cited 2024 March 20]. Available from: https://www.euromomo.eu/.
109. Health Protection Surveillance Centre. Influenza Surveillance Reports. Influenza Season 2019/2020 [Internet]. Dublin: HPSC; 2020 [cited 2024 May 20]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/surveillance/influenzasurveillancereports/previousinfluenzaseasonssurveillancereports/20192020season/.
110. European Centre for Disease Prevention and Contol - World Health Organisation Regional Office for Europe. Flu News Europe, Surveillance Description [Internet]. Europe: ECDC-WHO Regional Office for Europe; [cited 2023 September 01]. Available from: https://flunewseurope.org/AboutUs/SurveillanceDescription.
111. Matias G, Taylor RJ, Haguinet F, Schuck-Paim C, Lustig RL, Fleming DM. Modelling estimates of age-specific influenza-related hospitalisation and mortality in the United Kingdom. BMC public health. 2016;16:481.
112. Pumarola T, Díez-Domingo J, Martinón-Torres F, Redondo Margüello E, de Lejarazu Leonardo RO, Carmo M, et al. Excess hospitalizations and mortality associated with seasonal influenza in Spain, 2008-2018. BMC infectious diseases. 2023;23(1):86.
113. Lemaitre M, Fouad F, Carrat F, Crépey P, Gaillat J, Gavazzi G, et al. Estimating the burden of influenza-related and associated hospitalizations and deaths in France: An eight-season data study, 2010-2018. Influenza Other Respir Viruses. 2022;16(4):717-25.
114. Public Health England. Surveillance of influenza and other respiratory viruses in the UK Winter 2018 to 2019 [Internet]. UK: PHE; 2019 [updated 2019 May; cited 2023 September 01]. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20220401215804/https:/www.gov.uk/government/statistics/annual-flu-reports.
115. Health Protection Surveillance Centre. Seasonal Influenza Vaccine Uptake in Ireland, 2022-2023 [Internet]. Dublin: HPSC; 2024 [updated 2024 January 11; cited 2024 February 24]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/vaccination/influenzaandadults65yearsandolder/Seasonal%20Flu%20Vacc%20Uptake_report_Annual%202022_23_%20data%2004%2001%202024_1.1.pdf.
116. Health Service Executive. Pharmacy Circular 021/2011. National Seasonal Influenza Campaign: 2011 [Internet]. Dublin HSE; 2011 [cited 2023

November 16]. Available from: https://www.hse.ie/eng/staff/pcrs/circulars/pharmacy/seasonal%20flu%20campaign.pdf.
117. The Council of the European Union. Council Recommendation of 22 December 2009 on seasonal influenza vaccination (2009/1019/EU) [Internet]. Brussels: Official Journal of the European Union; 2009 [cited 2023 May 18]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009H1019&from=EN.
118. European Centre for Disease Prevention and Contol. Seasonal influenza vaccination and antiviral use in EU/EEA Member States - Overview of vaccine recommendations for 2017–2018 and vaccination coverage rates for 2015–2016 and 2016–2017 influenza seasons [Internet]. Stockholm: ECDC; 2018 [updated 2018 November; cited 2023 June 22]. Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-antiviral-use-eu-eea-member-states.
119. Public Health England. Surveillance of influenza and other seasonal respiratory viruses in the UK Winter 2020 to 2021 [Internet]. UK: PHE; 2021 [updated 2021 June; cited 2023 September 01]. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20220401215804/https://www.gov.uk/government/statistics/annual-flu-reports.
120. Public Health England. Surveillance of influenza and other respiratory viruses in the UK Winter 2019 to 2020 [Internet]. UK: PHE; 2020 [updated 2020 June; cited 2023 September 01]. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20220401215804/https://www.gov.uk/government/statistics/annual-flu-reports.
121. Health Service Executive. Seasonal Influenza [Internet]. Dublin: HSE; 2022 [updated 2022 December; cited 2023 October 31]. Available from: https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/influenza/.
122. Healthcare Pricing Office. HIPE Data Quality Statement 2023 [Internet]. Dublin: HPO; 2023 [updated 2023; cited 2023 October 25]. Available from: http://www.hipe.ie/DataQuality/HIPE%20Data%20Quality%20Statement%202023.pdf.
123. Health Service Executive. Costing and Pricing and Healthcare Pricing Office [Internet]. Dublin: HSE; 2023 [cited 2023 October 25]. Available from: https://www.hse.ie/eng/about/who/finance/nationalfinance/activity-based-funding-healthcare-pricing-office/.
124. Healthcare Pricing Office. Updating the Clinical Coding Classification 2024 [Internet]. Dublin: HPO; 2023 [updated 2023; cited 2023 October 31]. Available from: http://www.hpo.ie/seminar/pdf/2023/Jacqui_Curley_ABFConference_2023_Presentation1(F).pdf.
125. Healthcare Pricing Office. ABF 2023 Admitted Patient Price List: DRG Prices for Inpatients and Day Cases 2023 [Internet]. Dublin: HSE; 2023 [cited 2023 November 16]. Available from: http://hpo.ie/abf/ABF2023AdmittedPatientPriceListv1.pdf?ver=20230601.
126. Federici C, Cavazza M, Costa F, Jommi C. Health care costs of influenza-

related episodes in high income countries: A systematic review. PloS one. 2018;13(9):e0202787.
127. World Health Organization. A manual for estimating disease burden associated with seasonal influenza [Internet]. Geneva: WHO; 2015 [updated 2015 September 09; cited 2023 June 22]. Available from.
128. Moss JWE, Davidson C, Mattock R, Gibbons I, Mealing S, Carroll S. Quantifying the direct secondary health care cost of seasonal influenza in England. BMC public health. 2020;20(1):1464.
129. Foley C, Bloomer M, Hutchinson AM. Factors that influence intensive care admission decisions for older people: A systematic review. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses. 2023;36(2):274-84.
130. Central Statistics Office. PEA22 - Projected Population 2016 Based [Internet]. Cork: CSO; 2024 [updated 2020 November 09; cited 2023 December 21]. Available from: https://data.cso.ie/#.
131. Central Statistics Office. Population and Labour Force Projections 2017-2051. Population Projections Results [Internet]. Cork: CSO; 2024 [cited 2024 March 28]. Available from: https://www.cso.ie/en/releasesandpublications/ep/p-plfp/populationandlabourforceprojections2017-2051/populationprojectionsresults/.
132. Health Protection Surveillance Centre. Respiratory Virus Testing Capacity and Practices in Acute Hospital Settings in Ireland; Results from a National Laboratory Survey [Internet]. Dublin: HPSC; 2023 [updated 2023 November 06; cited 2023 December 21]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/publications/National%20Laboratory%20Survey%20Respiratory%20Virus%20Testing%20Report.pdf.
133. Centers for Disease Control and Prevention. Protect yourself from COVID-19, Flu, and RSV [Internet]. CDC; 2023 [cited 2023 September 27]. Available from: https://www.cdc.gov/respiratory-viruses/index.html.
134. Langer J, Welch VL, Moran MM, Cane A, Lopez SMC, Srivastava A, et al. High Clinical Burden of Influenza Disease in Adults Aged ≥ 65 Years: Can We Do Better? A Systematic Literature Review. Advances in therapy. 2023;40(4):1601-27.
135. Public Health England. Seasonal Influenza Vaccination Annual Report 2018/19: South West London: PHE; 2019 [cited 2024 13 Aug]. Available from: https://www.england.nhs.uk/wp-content/uploads/sites/6/2019/09/seasonal-vaccination-flu-report-18-19-final.pdf.
136. UK Health Security Agency. Seasonal influenza vaccine uptake in GP patients: Winter season 2022 to 2023 London: UKHSA; 2023 [updated June 2023; cited 2024 13 Aug]. Available from: https://assets.publishing.service.gov.uk/media/64d21e33a4045e000da84be5/GP-patients-flu-annual-report-2022-2023.pdf.
137. Health Service Executive. CoVax [Internet]. Ireland: HSE; 2023 [updated 2023 September 28; cited 2023 September 18]. Available from: https://www.hse.ie/eng/health/immunisation/hcpinfo/hsecovid19vms.html.
138. European Centre for Disease Prevention and Contol. Systematic review

update on the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory confirmed influenza in individuals aged 18 years and over [Internet]. Stockholm: ECDC; 2024 [updated 2024 April 08; cited 2024 April 16]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Systematic%20review%20update%20enhanced%20seasonal%20flu%20vaccines-final-with-covers.pdf.

139. Dugan HL, Henry C, Wilson PC. Aging and influenza vaccine-induced immunity. Cellular immunology. 2020;348:103998.
140. Reber AJ, Chirkova T, Kim JH, Cao W, Biber R, Shay DK, et al. Immunosenescence and Challenges of Vaccination against Influenza in the Aging Population. Aging and disease. 2012;3(1):68-90.
141. Lewis NM, Chung JR, Uyeki TM, Grohskopf L, Ferdinands JM, Patel MM. Interpretation of Relative Efficacy and Effectiveness for Influenza Vaccines. Clinical Infectious Diseases. 2021;75(1):170-5.
142. Rose A, Kissling E, Emborg H-D, Larrauri A, McMenamin J, Pozo F, et al. Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020. Eurosurveillance. 2020;25(10):2000153.
143. Rondy M, Kissling E, Emborg H-D, Gherasim A, Pebody R, Trebbien R, et al. Interim 2017/18 influenza seasonal vaccine effectiveness: combined results from five European studies. Eurosurveillance. 2018;23(9):18-00086.
144. Kissling E, Valenciano M. Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study. Eurosurveillance. 2016;21(6):30134.
145. Machado A, Mazagatos C, Dijkstra F, Kislaya I, Gherasim A, McDonald SA, et al. Impact of influenza vaccination programmes among the elderly population on primary care, Portugal, Spain and the Netherlands: 2015/16 to 2017/18 influenza seasons. Eurosurveillance. 2019;24(45):1900268.
146. Kissling E, Valenciano M, Buchholz U, Larrauri A, Cohen JM, Nunes B, et al. Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case–control study, influenza season 2012/13. Eurosurveillance. 2014;19(6):20701.
147. Kissling E, Valenciano M, Larrauri A, Oroszi B, Cohen JM, Nunes B, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case–control study. Eurosurveillance. 2013;18(5):20390.
148. Kissling E, Valenciano M, Falcão JM, Larrauri A, Widgren K, Pitigoi D, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. Eurosurveillance. 2009;14(44):19388.
149. Valenciano M, Kissling E, Cohen J-M, Oroszi B, Barret A-S, Rizzo C, et al. Estimates of Pandemic Influenza Vaccine Effectiveness in Europe, 2009–2010: Results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) Multicentre Case-Control Study. PLoS medicine. 2011;8(1):e1000388.
150. Kissling E, Valenciano M, Cohen JM, Oroszi B, Barret A-S, Rizzo C, et al. I-MOVE Multi-Centre Case Control Study 2010-11: Overall and Stratified Estimates of Influenza Vaccine Effectiveness in Europe. PloS one.

2011;6(11):e27622.
151. Minozzi S, Lytras T, Gianola S, Gonzalez-Lorenzo M, Castellini G, Galli C, et al. Comparative efficacy and safety of vaccines to prevent seasonal influenza: A systematic review and network meta-analysis. EClinicalMedicine. 2022;46:101331.
152. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
153. Bellino S, Bella A, Puzelli S, Di Martino A, Facchini M, Punzo O, et al. Moderate influenza vaccine effectiveness against A(H1N1)pdm09 virus, and low effectiveness against A(H3N2) subtype, 2018/19 season in Italy. Expert review of vaccines. 2019;18(11):1201-9.
154. Kissling E, Rondy M. Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-MOVE multicentre case control studies at primary care and hospital levels in Europe. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2017;22(7).
155. Mira-Iglesias A, López-Labrador FX, Baselga-Moreno V, Tortajada-Girbés M, Mollar-Maseres J, Carballido-Fernández M, et al. Influenza vaccine effectiveness against laboratory-confirmed influenza in hospitalised adults aged 60 years or older, Valencia Region, Spain, 2017/18 influenza season. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2019;24(31).
156. Pebody R, Whitaker H, Zhao H, Andrews N, Ellis J, Donati M, et al. Protection provided by influenza vaccine against influenza-related hospitalisation in ≥65 year olds: Early experience of introduction of a newly licensed adjuvanted vaccine in England in 2018/19. Vaccine. 2020;38(2):173-9.
157. Pebody RG, Whitaker H, Ellis J, Andrews N, Marques DFP, Cottrell S, et al. End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19. Vaccine. 2020;38(3):489-97.
158. Rondy M, Larrauri A, Casado I, Alfonsi V, Pitigoi D, Launay O, et al. 2015/16 seasonal vaccine effectiveness against hospitalisation with influenza A(H1N1)pdm09 and B among elderly people in Europe: results from the I-MOVE+ project. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2017;22(30).
159. Van Buynder PG, Konrad S, Van Buynder JL, Brodkin E, Krajden M, Ramler G, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. Vaccine. 2013;31(51):6122-8.
160. Domnich A, Panatto D, Pariani E, Napoli C, Chironna M, Manini I, et al. Relative effectiveness of the adjuvanted vs non-adjuvanted seasonal influenza vaccines against severe laboratory-confirmed influenza among hospitalized Italian older adults. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2022;125:164-9.
161. Frey SE, Reyes MR, Reynales H, Bermal NN, Nicolay U, Narasimhan V, et al.

Comparison of the safety and immunogenicity of an MF59®-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects. Vaccine. 2014;32(39):5027-34.
162. Li R, Fang H, Li Y, Liu Y, Pellegrini M, Podda A. Safety and immunogenicity of an MF59-adjuvanted subunit influenza vaccine in elderly Chinese subjects. Immunity & ageing : I & A. 2008;5:2.
163. Van Damme P, Arnou R, Kafeja F, Fiquet A, Richard P, Thomas S, et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomised comparative study. BMC infectious diseases. 2010;10:134.
164. Tsai TF, Crucitti A, Nacci P, Nicolay U, Cioppa GD, Ferguson J, et al. Explorations of clinical trials and pharmacovigilance databases of MF59®-adjuvanted influenza vaccines for associated cases of narcolepsy. Scandinavian Journal of Infectious Diseases. 2011;43(9):702-6.
165. Villa M, Black S, Groth N, Rothman KJ, Apolone G, Weiss NS, et al. Safety of MF59-adjuvanted influenza vaccination in the elderly: results of a comparative study of MF59-adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy. Am J Epidemiol. 2013;178(7):1139-45.
166. de Bruijn IA, Nauta J, Gerez L, Palache AM. The virosomal influenza vaccine Invivac: immunogenicity and tolerability compared to an adjuvanted influenza vaccine (Fluad in elderly subjects. Vaccine. 2006;24(44-46):6629-31.
167. Durando P, Fenoglio D, Boschini A, Ansaldi F, Icardi G, Sticchi L, et al. Safety and immunogenicity of two influenza virus subunit vaccines, with or without MF59 adjuvant, administered to human immunodeficiency virus type 1-seropositive and -seronegative adults. Clinical and vaccine immunology : CVI. 2008;15(2):253-9.
168. Frey S, Poland G, Percell S, Podda A. Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. Vaccine. 2003;21(27-30):4234-7.
169. Gasparini R, Pozzi T, Montomoli E, Fragapane E, Senatore F, Minutello M, et al. Increased immunogenicity of the MF59-adjuvanted influenza vaccine compared to a conventional subunit vaccine in elderly subjects. European journal of epidemiology. 2001;17(2):135-40.
170. Minutello M, Senatore F, Cecchinelli G, Bianchi M, Andreani T, Podda A, et al. Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in elderly subjects, immunized for three consecutive influenza seasons. Vaccine. 1999;17(2):99-104.
171. Ruf BR, Colberg K, Frick M, Preusche A. Open, randomized study to compare the immunogenicity and reactogenicity of an influenza split vaccine with an MF59-adjuvanted subunit vaccine and a virosome-based subunit vaccine in elderly. Infection. 2004;32(4):191-8.
172. Scheifele DW, McNeil SA, Ward BJ, Dionne M, Cooper C, Coleman B, et al. Safety, immunogenicity, and tolerability of three influenza vaccines in older adults: results of a randomized, controlled comparison. Human vaccines & immunotherapeutics. 2013;9(11):2460-73.
173. Seo YB, Choi WS, Lee J, Song JY, Cheong HJ, Kim WJ. Comparison of the

immunogenicity and safety of the conventional subunit, MF59-adjuvanted, and intradermal influenza vaccines in the elderly. Clinical and vaccine immunology : CVI. 2014;21(7):989-96.
174. de Lusignan S, Tsang RSM, Akinyemi O, Lopez Bernal J, Amirthalingam G, Sherlock J, et al. Adverse Events of Interest Following Influenza Vaccination in the First Season of Adjuvanted Trivalent Immunization: Retrospective Cohort Study. JMIR public health and surveillance. 2022;8(3):e25803.
175. Sindoni D, La Fauci V, Squeri R, Cannavò G, Bacilieri S, Panatto D, et al. Comparison between a conventional subunit vaccine and the MF59-adjuvanted subunit influenza vaccine in the elderly: an evaluation of the safety, tolerability and immunogenicity. Journal of preventive medicine and hygiene. 2009;50(2):121-6.
176. Balasubramani GK, Choi WS, Nowalk MP, Zimmerman RK, Monto AS, Martin ET, et al. Relative effectiveness of high dose versus standard dose influenza vaccines in older adult outpatients over four seasons, 2015-16 to 2018-19. Vaccine. 2020;38(42):6562-9.
177. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. The New England journal of medicine. 2014;371(7):635-45.
178. Doyle JD, Beacham L, Martin ET, Talbot HK, Monto A, Gaglani M, et al. Relative and Absolute Effectiveness of High-Dose and Standard-Dose Influenza Vaccine Against Influenza-Related Hospitalization Among Older Adults-United States, 2015-2017. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;72(6):995-1003.
179. Chang LJ, Meng Y, Janosczyk H, Landolfi V, Talbot HK. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: A phase 3 randomized clinical trial. Vaccine. 2019;37(39):5825-34.
180. Chen J-Y, Hsieh S-M, Hwang S-J, Liu C-S, Li X, Fournier M, et al. Immunogenicity and safety of high-dose quadrivalent influenza vaccine in older adults in Taiwan: A phase III, randomized, multi-center study. Vaccine. 2022;40(45):6450-4.
181. DiazGranados CA, Saway W, Gouaux J, Baron M, Baker J, Denis M, et al. Safety and immunogenicity of high-dose trivalent inactivated influenza vaccine in adults 50-64 years of age. Vaccine. 2015;33(51):7188-93.
182. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. The Journal of infectious diseases. 2009;200(2):172-80.
183. Pepin S, Nicolas JF, Szymanski H, Leroux-Roels I, Schaum T, Bonten M, et al. Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized Phase III trial. Human vaccines & immunotherapeutics. 2021;17(12):5475-86.
184. Sanchez L, Nakama T, Nagai H, Matsuoka O, Inoue S, Inoue T, et al. Superior immunogenicity of high-dose quadrivalent inactivated influenza vaccine versus

Standard-Dose vaccine in Japanese Adults ≥ 60 years of age: Results from a phase III, randomized clinical trial. Vaccine. 2023;41(15):2553-61.
185. Arya DP, Said MA, Izurieta HS, Perez-Vilar S, Zinderman C, Wernecke M, et al. Surveillance for Guillain-Barré syndrome after 2015-2016 and 2016-2017 influenza vaccination of Medicare beneficiaries. Vaccine. 2019;37(43):6543-9.
186. Layton JB, McGrath LJ, Sahrmann JM, Ma Y, Dharnidharka VR, O'Neil C, et al. Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease. Vaccine. 2020;38(33):5178-86.
187. Caldera F, Hillman L, Saha S, Wald A, Grimes I, Zhang Y, et al. Immunogenicity of High Dose Influenza Vaccine for Patients with Inflammatory Bowel Disease on Anti-TNF Monotherapy: A Randomized Clinical Trial. Inflammatory bowel diseases. 2020;26(4):593-602.
188. Noh JY, Jang YS, Lee SN, Choi MJ, Yoon JG, Yu DH, et al. Randomized, single-blind, active-controlled phase I clinical trial to evaluate the immunogenicity and safety of GC3114 (high-dose, quadrivalent influenza vaccine) in healthy adults. Vaccine. 2019;37(36):5171-6.
189. Tsang P, Gorse GJ, Strout CB, Sperling M, Greenberg DP, Ozol-Godfrey A, et al. Immunogenicity and safety of Fluzone(®) intradermal and high-dose influenza vaccines in older adults ≥65 years of age: a randomized, controlled, phase II trial. Vaccine. 2014;32(21):2507-17.
190. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine. 2007;25(44):7656-63.
191. Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Archives of internal medicine. 2006;166(10):1121-7.
192. Pillet S, Couillard J, Trépanier S, Poulin JF, Yassine-Diab B, Guy B, et al. Immunogenicity and safety of a quadrivalent plant-derived virus like particle influenza vaccine candidate-Two randomized Phase II clinical trials in 18 to 49 and ≥50 years old adults. PloS one. 2019;14(6):e0216533.
193. Bruxvoort KJ, Luo Y, Ackerson B, Tanenbaum HC, Sy LS, Gandhi A, et al. Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017-2018. Vaccine. 2019;37(39):5807-11.
194. Klein NP, Fireman B, Goddard K, Zerbo O, Asher J, Zhou J, et al. Vaccine effectiveness of cell-culture relative to egg-based inactivated influenza vaccine during the 2017-18 influenza season. PloS one. 2020;15(2):e0229279.
195. Martin ET, Cheng C, Petrie JG, Alyanak E, Gaglani M, Middleton DB, et al. Low Influenza Vaccine Effectiveness Against A(H3N2)-Associated Hospitalizations in 2016-2017 and 2017-2018 of the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN). The Journal of infectious diseases. 2021;223(12):2062-71.
196. Ehrlich HJ, Berezuk G, Fritsch S, Aichinger G, Singer J, Portsmouth D, et al. Clinical development of a Vero cell culture-derived seasonal influenza vaccine. Vaccine. 2012;30(29):4377-86.
197. Frey S, Vesikari T, Szymczakiewicz-Multanowska A, Lattanzi M, Izu A, Groth N, et al. Clinical efficacy of cell culture–derived and egg-derived inactivated

subunit influenza vaccines in healthy adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;51(9):997-1004.
198. Groth N, Montomoli E, Gentile C, Manini I, Bugarini R, Podda A. Safety, tolerability and immunogenicity of a mammalian cell-culture-derived influenza vaccine: a sequential Phase I and Phase II clinical trial. Vaccine. 2009;27(5):786-91.
199. Halperin SA, Smith B, Mabrouk T, Germain M, Trépanier P, Hassell T, et al. Safety and immunogenicity of a trivalent, inactivated, mammalian cell culture-derived influenza vaccine in healthy adults, seniors, and children. Vaccine. 2002;20(7-8):1240-7.
200. Song JY, Cheong HJ, Lee J, Woo HJ, Wie SH, Lee JS, et al. Immunogenicity and safety of a cell culture-derived inactivated trivalent influenza vaccine (NBP607): A randomized, double-blind, multi-center, phase 3 clinical trial. Vaccine. 2015;33(41):5437-44.
201. Szymczakiewicz-Multanowska A, Groth N, Bugarini R, Lattanzi M, Casula D, Hilbert A, et al. Safety and immunogenicity of a novel influenza subunit vaccine produced in mammalian cell culture. The Journal of infectious diseases. 2009;200(6):841-8.
202. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. The New England journal of medicine. 2017;376(25):2427-36.
203. Zimmerman RK, Dauer K, Clarke L, Nowalk MP, Raviotta JM, Balasubramani GK. Vaccine effectiveness of recombinant and standard dose influenza vaccines against outpatient illness during 2018-2019 and 2019-2020 calculated using a retrospective test-negative design. Human vaccines & immunotherapeutics. 2023;19(1):2177461.
204. Hsiao A, Yee A, Fireman B, Hansen JR, Lewis N, Klein NP. 2322. Effectiveness of Recombinant Influenza Vaccine vs. Standard Dose Inactivated Influenza Vaccines Against Hospitalized Influenza-Related Outcomes in Adults: A Cluster Randomized Trial: Open Forum Infect Dis. 2022 Dec 15;9(Suppl 2):ofac492.153. doi: 10.1093/ofid/ofac492.153. eCollection 2022 Dec.; 2022.
205. Baxter R, Patriarca PA, Ensor K, Izikson R, Goldenthal KL, Cox MM. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. Vaccine. 2011;29(12):2272-8.
206. Treanor JJ, El Sahly H, King J, Graham I, Izikson R, Kohberger R, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: a randomized, placebo-controlled trial. Vaccine. 2011;29(44):7733-9.
207. Hansen J, Goddard K, Timbol J, Zhang L, Lewis N, Dunkle L, et al. Safety of Recombinant Influenza Vaccine Compared to Inactivated Influenza Vaccine in Adults: An Observational Study. Open forum infectious diseases. 2020;7(6):ofaa179.
208. Dunkle LM, Izikson R, Patriarca PA, Goldenthal KL, Muse D, Cox MMJ. Randomized Comparison of Immunogenicity and Safety of Quadrivalent

Recombinant Versus Inactivated Influenza Vaccine in Healthy Adults 18-49 Years of Age. The Journal of infectious diseases. 2017;216(10):1219-26.
209. Keitel WA, Treanor JJ, El Sahly HM, Gilbert A, Meyer AL, Patriarca PA, et al. Comparative immunogenicity of recombinant influenza hemagglutinin (rHA) and trivalent inactivated vaccine (TIV) among persons > or =65 years old. Vaccine. 2009;28(2):379-85.
210. Treanor JJ, Schiff GM, Couch RB, Cate TR, Brady RC, Hay CM, et al. Dose-related safety and immunogenicity of a trivalent baculovirus-expressed influenza-virus hemagglutinin vaccine in elderly adults. The Journal of infectious diseases. 2006;193(9):1223-8.
211. Izikson R, Leffell DJ, Bock SA, Patriarca PA, Post P, Dunkle LM, et al. Randomized comparison of the safety of Flublok(®) versus licensed inactivated influenza vaccine in healthy, medically stable adults ≥ 50 years of age. Vaccine. 2015;33(48):6622-8.
212. Pillsbury AJ, Fathima P, Quinn HE, Cashman P, Blyth CC, Leeb A, et al. Comparative Postmarket Safety Profile of Adjuvanted and High-Dose Influenza Vaccines in Individuals 65 Years or Older. JAMA Network Open. 2020;3(5):e204079-e.
213. Woo EJ, Moro PL. Post-marketing safety surveillance of high-dose quadrivalent influenza vaccine: Reports to the Vaccine Adverse Event Reporting System. Vaccine. 2022;40(7):1026-30.
214. Amicizia D, Domnich A, Lai PL, Orsi A, Icardi G, Tkach-Motulyak O, et al. Enhanced passive safety surveillance of the MF59-adjuvanted quadrivalent influenza vaccine in the elderly during the 2021/22 influenza season. Human vaccines & immunotherapeutics. 2023;19(1):2190279.
215. McMenamin ME, Bond HS, Sullivan SG, Cowling BJ. Estimation of Relative Vaccine Effectiveness in Influenza: A Systematic Review of Methodology. Epidemiology (Cambridge, Mass). 2022;33(3):334-45.
216. Ultsch B, Damm O, Beutels P, Bilcke J, Brüggenjürgen B, Gerber-Grote A, et al. Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community. PharmacoEconomics. 2016;34(3):227-44.
217. Loperto I, Simonetti A, Nardone A, Triassi M. Use of adjuvanted trivalent influenza vaccine in older-age adults: a systematic review of economic evidence. Human vaccines & immunotherapeutics. 2019;15(5):1035-47.
218. Colrat F, Thommes E, Largeron N, Alvarez FP. Economic evaluation of high-dose inactivated influenza vaccine in adults aged ≥65 years: A systematic literature review. Vaccine. 2021;39:A42-A50.
219. Loong D, Pham B, Amiri M, Saunders H, Mishra S, Radhakrishnan A, et al. Systematic Review on the Cost-Effectiveness of Seasonal Influenza Vaccines in Older Adults. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2022;25(8):1439-58.
220. Covidence. Covidence software. Melbourne, Australia: Covidence; 2022.
221. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. PharmacoEconomics. 2006;24(4):355-71.
222. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et

al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.
223. Crépey P, Redondo E, Díez-Domingo J, Ortiz de Lejarazu R, Martinón-Torres F, Gil de Miguel Á, et al. From trivalent to quadrivalent influenza vaccines: Public health and economic burden for different immunization strategies in Spain. PloS one. 2020;15(5):e0233526.
224. Redondo E, Drago G, López-Belmonte JL, Guillén JM, Bricout H, Alvarez FP, et al. Cost-utility analysis of influenza vaccination in a population aged 65 years or older in Spain with a high-dose vaccine versus an adjuvanted vaccine. Vaccine. 2021;39(36):5138-45.
225. Mattock R, Gibbons I, Moss J, Mealing S, Largeron N, Carroll S, et al. Cost-effectiveness of high dose versus adjuvanted trivalent influenza vaccines in England and Wales. J Med Econ. 2021;24(1):1261-71.
226. Kohli MA, Maschio M, Mould-Quevedo JF, Drummond M, Weinstein MC. The cost-effectiveness of an adjuvanted quadrivalent influenza vaccine in the United Kingdom. Human vaccines & immunotherapeutics. 2021;17(11):4603-10.
227. Rumi F, Basile M, Cicchetti A. Analisi di costo-efficacia e budget impact per il vaccino antinfluenzale quadrivalente ad alto dosaggio nella popolazione anziana italiana. Global & regional health technology assessment. 2021;8:105-13.
228. Tavares D, Mouriño H, Rodríguez CA, Saborido CM. Cost Effectiveness of Quadrivalent Versus Trivalent Inactivated Influenza Vaccines for the Portuguese Elderly Population. Vaccines. 2022;10(8).
229. Ruiz-Aragón J, Márquez-Peláez S, Gani R, Alvarez P, Guerrero-Ludueña R. Cost-Effectiveness and Burden of Disease for Adjuvanted Quadrivalent Influenza Vaccines Compared to High-Dose Quadrivalent Influenza Vaccines in Elderly Patients in Spain. Vaccines. 2022;10.
230. Nguyen VH, Roy B. Modelling the Economic Impact of lnfluenza Vaccine Programs with the Cell-Based Quadrivalent Influenza Vaccine and Adjuvanted Trivalent Influenza Vaccine in Canada. Vaccines [Internet]. 2022 2022/08//; 10(8):1257. Available from: https://doi.org/10.3390/vaccines10081257.
231. Kohli MA, Maschio M, Cartier S, Mould-Quevedo J, Fricke F-U. The Cost-Effectiveness of Vaccination of Older Adults with an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Other Available Quadrivalent Vaccines in Germany. Vaccines. 2022;10(9):1386.
232. Fochesato A, Sottile S, Pugliese A, Márquez-Peláez S, Toro-Diaz H, Gani R, et al. An Economic Evaluation of the Adjuvanted Quadrivalent Influenza Vaccine Compared with Standard-Dose Quadrivalent Influenza Vaccine in the Spanish Older Adult Population. Vaccines [Internet]. 2022 2022/08//; 10(8):1360. Available from: https://doi.org/10.3390/vaccines10081360.
233. Choi MJ, Shin G, Kang D, Lim J-O, Kim Y-K, Choi WS, et al. Cost-Effectiveness of Influenza Vaccination Strategies in Adults: Older Adults Aged ≥65 Years, Adults Aged 50–64 Years, and At-Risk Adults Aged 19–64 Years. Vaccines. 2022;10(3):445.
234. Bianculli PM, Bellier L, Mangado IO, Pérez CG, Mieres G, Lazarov L, et al. Switching from trivalent to quadrivalent inactivated influenza vaccines in

Uruguay: a cost-effectiveness analysis. Human vaccines & immunotherapeutics. 2022;18(5):2050653.
235. Sandmann FG, van Leeuwen E, Bernard-Stoecklin S, Casado I, Castilla J, Domegan L, et al. Health and economic impact of seasonal influenza mass vaccination strategies in European settings: A mathematical modelling and cost-effectiveness analysis. Vaccine. 2022;40(9):1306-15.
236. Nguyen VH, Ashraf M, Mould-Quevedo JF. Cost-Effectiveness of the Use of Adjuvanted Quadrivalent Seasonal Influenza Vaccine in Older Adults in Ireland. Vaccines. 2023;11(5):933.
237. Marbaix S, Dauby N, Mould-Quevedo J. Cost-effectiveness of the adjuvanted quadrivalent influenza vaccine in the elderly Belgian population. Expert review of vaccines. 2023;22(1):608-19.
238. Kim DeLuca E, Gebremariam A, Rose A, Biggerstaff M, Meltzer MI, Prosser LA. Cost-effectiveness of routine annual influenza vaccination by age and risk status. Vaccine. 2023;41(29):4239-48.
239. Jacob J, Biering-Sørensen T, Holger Ehlers L, Edwards CH, Mohn KG, Nilsson A, et al. Cost-Effectiveness of Vaccination of Older Adults with an MF59(®)-Adjuvanted Quadrivalent Influenza Vaccine Compared to Standard-Dose and High-Dose Vaccines in Denmark, Norway, and Sweden. Vaccines. 2023;11(4).
240. Alvarez FP, Chevalier P, Borms M, Bricout H, Marques C, Soininen A, et al. Cost-effectiveness of influenza vaccination with a high dose quadrivalent vaccine of the elderly population in Belgium, Finland, and Portugal. J Med Econ. 2023;26(1):710-9.
241. Ruiz-Aragón J, Márquez-Peláez S. An Economic Comparison in the Elderly of Adjuvanted Quadrivalent Influenza Vaccine with Recombinant Quadrivalent Influenza Vaccine in Spain. Vaccines. 2023;11(2):427.
242. Chit A, Roiz J, Aballea S. An Assessment of the Expected Cost-Effectiveness of Quadrivalent Influenza Vaccines in Ontario, Canada Using a Static Model. PloS one. 2015;10(7):e0133606.
243. World Health Organization. Guidance on the economic evaluation of influenza vaccination [Internet]. Geneva: WHO; 2016 [updated 2016 September; cited 2023 September 21]. Available from: https://iris.who.int/bitstream/handle/10665/250086/WHO-IVB-16.05-eng.pdf;sequence=1.
244. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, et al. Vaccines for preventing influenza in the elderly. Cochrane Database of Systematic Reviews. 2018(2).
245. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. The Cochrane database of systematic reviews. 2018;2(2):Cd001269.
246. DiazGranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. Vaccine. 2012;31(1):49-57.
247. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC medicine. 2013;11:153.
248. Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT,

et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. The Lancet Infectious diseases. 2016;16(8):942-51.
249. Sciensano. Influenza. Numbers [Internet]. Brussels: Sciensano; 2023 [cited 2023 February]. Available from: https://www.sciensano.be/en/node/464.
250. Fleming DM, Andrews NJ, Ellis JS, Bermingham A, Sebastianpillai P, Elliot AJ, et al. Estimating influenza vaccine effectiveness using routinely collected laboratory data. Journal of epidemiology and community health. 2010;64(12):1062-7.
251. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. BMC medicine. 2015;13:236.
252. Clements KM, Meier G, McGarry LJ, Pruttivarasin N, Misurski DA. Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States. Human vaccines & immunotherapeutics. 2014;10(5):1171-80.
253. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. Jama. 1994;272(21):1661-5.
254. Calabrò GE, Boccalini S, Panatto D, Rizzo C, Di Pietro ML, Abreha FM, et al. The New Quadrivalent Adjuvanted Influenza Vaccine for the Italian Elderly: A Health Technology Assessment. International Journal of Environmental Research and Public Health. 2022;19(7):4166.
255. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. The Cochrane database of systematic reviews. 2012;2012(8):Cd004879.
256. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. The Lancet Infectious diseases. 2012;12(1):36-44.
257. Coleman BL, Sanderson R, Haag MDM, McGovern I. Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis. Influenza Other Respir Viruses. 2021;15(6):813-23.
258. Puig-Barberà J, Natividad-Sancho A, Calabuig-Pérez J, Lluch-Rodrigo JA, Pastor-Villalba E, Martínez-Úbeda S, et al. MF59-adjuvanted and virosomal influenza vaccines for preventing influenza hospitalization in older people: Comparative effectiveness using the Valencia health care information system. Vaccine. 2013;31(37):3995-4002.
259. Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of Adjuvanted Influenza Vaccination in Elderly Subjects in Northern Italy. American Journal of Epidemiology. 2012;176(6):527-33.
260. Thorrington D, van Leeuwen E, Ramsay M, Pebody R, Baguelin M. Assessing optimal use of the standard dose adjuvanted trivalent seasonal influenza vaccine in the elderly. Vaccine. 2019;37(15):2051-6.
261. Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. Vaccine. 2017;35(4):513-20.

262. Pebody RG, Whitaker H, Ellis J, Andrews N, Marques DFP, Cottrell S, et al. End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19. Vaccine. 2020;38(3):489-97.
263. European Medicines Agency. Assessment report. Fluad Tetra [Internet]. Amsterdam: EMA; 2020 [updated 2020 March 26; cited 2023 September 27]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/fluad-tetra-epar-public-assessment-report_en.pdf.
264. Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert review of vaccines. 2018;17(5):435-43.
265. Izurieta HS, Lu M, Kelman J, Lu Y, Lindaas A, Loc J, et al. Comparative Effectiveness of Influenza Vaccines Among US Medicare Beneficiaries Ages 65 Years and Older During the 2019–2020 Season. Clinical Infectious Diseases. 2020;73(11):e4251-e9.
266. Nguyen VH, Hilsky Y, Mould-Quevedo J. The Epidemiological and Economic Impact of a Cell-Based Quadrivalent Influenza Vaccine in Adults in the US: A Dynamic Modeling Approach. Vaccines. 2021;9(10):1095.
267. York Health Economics Consortium. Net Monetary Benefit York: YHEC; 2016 [cited 2023 September 26]. Available from: https://yhec.co.uk/glossary/net-monetary-benefit/.
268. World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition. Geneva: 2019 Contract No.: Licence: CC BY-NC-SA 3.0 IGO.
269. Pradas-Velasco R, Antoñanzas-Villar F, Martínez-Zárate MP. Dynamic Modelling of Infectious Diseases. PharmacoEconomics. 2008;26(1):45-56.
270. Annemans L, Beutels P, Bloom DE, De Backer W, Ethgen O, Luyten J, et al. Economic Evaluation of Vaccines: Belgian Reflections on the Need for a Broader Perspective. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2021;24(1):105-11.
271. Avşar TS, Yang X, Lorgelly P. How is the Societal Perspective Defined in Health Technology Assessment? Guidelines from Around the Globe. PharmacoEconomics. 2023;41(2):123-38.
272. Fayanju OM, Haukoos JS, Tseng JF. CHEERS Reporting Guidelines for Economic Evaluations. JAMA surgery. 2021;156(7):677-8.
273. Health Information and Quality Authority. Guidelines for the Economic Evaluation of Health Technologies in Ireland. Cork: HIQA, 2020.
274. York Health Economics Consortium. Discount rate [Internet]. York: YHEC; 2016 [updated 2016; cited 2023 November 15]. Available from: https://yhec.co.uk/glossary/discount-rate/.
275. Khorasani E, Davari M, Kebriaeezadeh A, Fatemi F, Akbari Sari A, Varahrami V. A comprehensive review of official discount rates in guidelines of health economic evaluations over time: the trends and roots. The European Journal of Health Economics. 2022;23(9):1577-90.
276. Health Protection Surveillance Centre. Seasonal Influenza Vaccine Uptake [Internet]. Dublin: HPSC; 2023 [cited 2023 June 22]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/vaccination/.

277. Su Z, Cheshmehzangi A, McDonnell D, da Veiga CP, Xiang YT. Mind the "Vaccine Fatigue". Frontiers in immunology. 2022;13:839433.
278. Citizens Information. GP visit cards [Internet]. Ireland: 2023 [updated 2023 September 21; cited 2023 October 11]. Available from: https://www.citizensinformation.ie/en/health/medical-cards-and-gp-visit-cards/gp-visit-cards/.
279. Comber L, E OM, Jordan K, Hawkshaw S, Marshall L, O'Neill M, et al. Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Reviews in medical virology. 2023;33(3):e2330.
280. Xie F, Zhou T. Industry sponsorship bias in cost effectiveness analysis: registry based analysis. BMJ (Clinical research ed). 2022;377:e069573.
281. Zhou T, Xie F. Sponsorship bias in oncology cost effectiveness analysis. J Clin Epidemiol. 2023;156:22-9.
282. Bilcke J, Verelst F, Beutels P. Sponsorship Bias in Base-Case Values and Uncertainty Bounds of Health Economic Evaluations? A Systematic Review of Herpes Zoster Vaccination. Medical decision making : an international journal of the Society for Medical Decision Making. 2018;38(6):730-45.
283. Catalá-López F, Sanfélix-Gimeno G, Ridao M, Peiró S. When are statins cost-effective in cardiovascular prevention? A systematic review of sponsorship bias and conclusions in economic evaluations of statins. PloS one. 2013;8(7):e69462.
284. Health Protection Surveillance Centre. Respiratory Virus Notification Data Hub [Internet]. Dublin: HPSC; 2024 [updated 2024; cited 2024 March 19]. Available from: https://respiratoryvirus.hpsc.ie/.
285. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS medicine. 2008;5(3):e74.
286. Central Statistics Office. PEA11 - Population estimates from 1926 [Internet]. Cork: CSO; 2024 [updated 2023 September 25; cited 2024 March 19]. Available from: https://ws.cso.ie/public/api.restful/PxStat.Data.Cube_API.ReadDataset/PEA11/XLSX/2007/en.
287. Central Statistics Office. VSA32 - Period Life Expectancy [Internet]. Cork: Central Statistics Office; 2024 [updated 2020 September 29; cited 2024 April 24]. Available from: https://ws.cso.ie/public/api.restful/PxStat.Data.Cube_API.ReadDataset/VSA32/XLSX/2007/en.
288. Goeyvaerts N, Willem L, Van Kerckhove K, Vandendijck Y, Hanquet G, Beutels P, et al. Estimating dynamic transmission model parameters for seasonal influenza by fitting to age and season-specific influenza-like illness incidence. Epidemics. 2015;13:1-9.
289. Wiedermann U, Garner-Spitzer E, Wagner A. Primary vaccine failure to routine vaccines: Why and what to do? Human vaccines & immunotherapeutics. 2016;12(1):239-43.
290. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH,

Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMJ (Clinical research ed). 2022;376:e067975.
291. R Core Team. R: A language and environment for statistical computing. MSOR connections. 2014;1.
292. Microsoft 365. Microsoft Excel. Redmond, Washington, USA: Microsoft; 2013.
293. Mauskopf J, Standaert B, Connolly MP, Culyer AJ, Garrison LP, Hutubessy R, et al. Economic Analysis of Vaccination Programs: An ISPOR Good Practices for Outcomes Research Task Force Report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(10):1133-49.
294. Health Information and Quality Authority. Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. Cork: HIQA, 2018.
295. Health Protection Surveillance Centre. Respiratory Virus Notification Data Hub. Epidemiology of Influenza in Ireland [Internet]. Dublin: HPSC; 2024 [updated 2024 March 23; cited 2024 March 25]. Available from: https://respiratoryvirus.hpsc.ie/pages/influenza.
296. Hobbins A, Barry L, Kelleher D, O'Neill C. The health of the residents of Ireland: Population norms for Ireland based on the EQ-5D-5L descriptive system - a cross sectional study. HRB open research. 2018;1:22.
297. Hollmann M, Garin O, Galante M, Ferrer M, Dominguez A, Alonso J. Impact of influenza on health-related quality of life among confirmed (H1N1)2009 patients. PloS one. 2013;8(3):e60477.
298. Central Statistics Office. Consumer Price Index [Internet]. Cork: CSO; 2024 [updated 2024 March 14; cited 2024 March 26]. Available from: https://www.cso.ie/en/statistics/prices/consumerpriceindex/.
299. Health Service Executive. PCRS Publications: Reporting and Open Data [Internet]. Dublin: HSE; 2024 [updated 2024; cited 2024 March 26]. Available from: https://www.sspcrs.ie/portal/annual-reporting/report/eligibility.
300. Meier GC, Watkins J, McEwan P, Pockett RD. Resource use and direct medical costs of acute respiratory illness in the UK based on linked primary and secondary care records from 2001 to 2009. PloS one. 2020;15(8):e0236472.
301. Ehlken B, Anastassopoulou A, Hain J, Schröder C, Wahle K. Cost for physician-diagnosed influenza and influenza-like illnesses on primary care level in Germany – results of a database analysis from May 2010 to April 2012. BMC public health. 2015;15(1):578.
302. Smith S, Jiang J, Normand C, O'Neill C. Unit costs for non-acute care in Ireland 2016-2019. HRB open research. 2021;4:39.
303. Health Service Executive. Antibiotic Prescribing - Conditions and Treatments [Internet]. Dublin: HSE; 2023 [updated 2023 October; cited 2024 March 26]. Available from: https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/.
304. National Centre for Pharmacoeconomics. Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluations Version 3.2 [Internet]. Dublin: NCPE; 2024 [updated 2023 May 17; cited 2024 February 27]. Available from: https://www.ncpe.ie/wp-content/uploads/2023/05/Guidelines-for-Inclusion-of-Drug-Costs-in-Pharmacoeconomic-Evaluations-v3.2.pdf.

305. Bilcke J, Coenen S, Beutels P. Influenza-like-illness and clinically diagnosed flu: disease burden, costs and quality of life for patients seeking ambulatory care or no professional care at all. PloS one. 2014;9(7):e102634.
306. Krol M, Brouwer W. How to estimate productivity costs in economic evaluations. PharmacoEconomics. 2014;32(4):335-44.
307. Central Statistics Office. Labour Force Survey Quarter 4 2023 [Internet]. Cork: CSO; 2024 [updated 2024 February 22; cited 2024 March 26]. Available from: https://www.cso.ie/en/releasesandpublications/ep/p-lfs/labourforcesurveyquarter42023/.
308. Central Statistics Office. Earnings Analysis using Administrative Data Sources 2022 [Internet]. Cork: CSO; 2023 [updated 2023 October 10; cited 2024 March 26]. Available from: https://www.cso.ie/en/releasesandpublications/ep/p-eaads/earningsanalysisusingadministrativedatasources2022/age/.
309. Central Statistics Office. Irish Life Tables [Internet]. Cork: CSO; 2024 [cited 2024 March 26]. Available from: https://www.cso.ie/en/statistics/birthsdeathsandmarriages/irishlifetables/.
310. British National Formulary. British National Formulary, [Internet]. London: NICE; 2023 [cited 2023 November 30]. Available from: https://bnf.nice.org.uk/.
311. Ministry of Health (Spain). Specific administrative clauses of the framework agreement for the selection of vaccine suppliers against seasonal flu for certain contracting bodies of the general administration of the State National Institute of Health Managmenet (INGESA) and the cities of Ceuta and Melilla and various community autonomous units. [Internet]. Madrid: Ministry of Health (Spain); 2021 [updated 2021 March 26; cited 2023 October 19. Available from: DOC20210419131140PCAP+Gripe+2021-2025.pdf (contrataciondelestado.es)
312. Hatswell AJ, Bullement A, Briggs A, Paulden M, Stevenson MD. Probabilistic Sensitivity Analysis in Cost-Effectiveness Models: Determining Model Convergence in Cohort Models. PharmacoEconomics. 2018;36(12):1421-6.
313. Revenue (Irish Tax and Customs). Current VAT Rates [Internet]. Dublin: Office of the Revenue Commissioners; 2024 [updated 2024 January 01; cited 2024 March 28]. Available from: https://www.revenue.ie/en/corporate/information-about-revenue/role-of-revenue/index.aspx.
314. Jaouimaa FZ, Dempsey D, Van Osch S, Kinsella S, Burke K, Wyse J, et al. An age-structured SEIR model for COVID-19 incidence in Dublin, Ireland with framework for evaluating health intervention cost. PloS one. 2021;16(12):e0260632.
315. European Observatory on Health Systems and Policies. The organization and delivery of vaccination services in the European Union [Internet]. Brussels: WHO; 2018 [updated 2018; cited 2023 November 02]. Available from: https://health.ec.europa.eu/system/files/2018-11/2018_vaccine_services_en_0.pdf.
316. HSE National Immunisation Office. Driving Change in Immunisation - The Role of the National Immunisation Office 2005-2011. [Internet]. Dublin: HSE

National Immunisation Office; 2012 [updated 2012 June; cited 2023 July 13]. Available from: https://www.hse.ie/eng/health/immunisation/infomaterials/drivingchangeinimmunisation.pdf.

317. Marron L, Barrett T,, Migone C,, Jessop L,, Keegan A,. Flu vaccine errors following introduction of the adjuvant flu vaccine during the 2021/2022 flu season [Internet]. Dublin: HSE National Immunisation Office; 2022 [cited 2024 July 18]. Available from: https://www.hse.ie/eng/health/immunisation/news/17-louise-marron-flu-vaccine-errors-following-introduction-of-flu-vaccine1.pdf.
318. Central Statistics Office. PEB07 - Projected Population [Internet]. Cork: CSO; 2021 [updated 2021 March 15; cited 2023 June 20]. Available from: https://data.cso.ie/#.
319. Central Statistics Office. Census of Population 2016 - Profile 3 An Age Profile of Ireland. Age groups [Internet]. Cork: CSO; 2017 [updated 2017 July 06; cited 2023 July 13]. Available from: https://www.cso.ie/en/releasesandpublications/ep/p-cp3oy/cp3/agr/.
320. Central Statistics Office. FY006B - Population [Internet]. Cork: CSO; 2023 [updated 2023 May 30; cited 2024 April 24]. Available from: https://data.cso.ie/.
321. Central Statistics Office. Census of Population 2022 - Summary Results. Population changes [Internet]. Cork: CSO; 2023 [updated 2023 May 30; cited 2023 November 13]. Available from: https://www.cso.ie/en/releasesandpublications/ep/p-cpsr/censusofpopulation2022-summaryresults/populationchanges/.
322. Royal College of Physicians of Ireland. National Immunisation Advisory Committee Immunisation Guidelines. Chapter 01. General Information. [Internet]. Dublin: Royal College of Physicians; 2015 [updated 2015 August; cited 2023 July 13]. Available from: https://rcpi.access.preservica.com/uncategorized/IO_dc1318eb-b51a-4bb2-92fe-05a5b934401b/.
323. Royal College of Physicians of Ireland. National Immunisation Advisory Committee Immunisation Guidelines. Anaphylaxis [Internet]. Dublin: Royal College of Physicians of Ireland. National Immunisation Advisory Committee (NIAC); 2023 [updated 2023 February 23; cited 2024 May 20]. Available from: https://rcpi.access.preservica.com/uncategorized/IO_a36f9e4b-4c80-432d-8264-546089359925/.
324. HSE National Immunisation Office. Supporting Information For Vaccinations In General Practice [Internet]. Dublin: HSE National Immunisation Office; 2022 [updated 2022 December; cited 2024 April 22]. Available from: https://www.hse.ie/eng/health/immunisation/infomaterials/gpsupportingdocpci.pdf.
325. Pharmaceutical Society of Ireland. Training for Pharmacists for the Supply and Administration of Vaccinations [Internet]. Dublin: PSI; 2023 [updated 2023; cited 2024 March 04]. Available from: https://www.thepsi.ie/gns/education/Training_for_Pharmacists_Vaccinations.aspx.

326. O'Donnell S. Pharmacy seasonal influenza vaccination service [Internet]. Dublin: IPU Review; 2023 [updated 2023 July; cited 2024 March 04]. Available from: https://ipu.ie/wp-content/uploads/2023/07/Pharmacy-seasonal-influenza-vaccination-service.pdf.
327. Health Protection Surveillance Centre. Seasonal Influenza Vaccine uptake in Ireland in persons aged 65 years and older attending GP Clinics and pharmacies for vaccination [Internet]. Dublin: HPSC; 2021 [updated 2021 October 08; cited 2023 July 14]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/vaccination/influenzaandadults65yearsandolder/Seasonal%20Flu%20Vaccination%20Uptake_65%20report_Sep18-Aug%2019.docx.pdf.
328. Health Protection Surveillance Centre. Report on the Uptake of the Influenza Vaccine for Health Care Workers (HCWs) and residents in Long-Term/Residential Care Facilities (LTCFs). 2021-2022 Season [Internet]. 2022 [updated 2022 August; cited 2024 March 04]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/surveillance/vaccineuptakeinhcwsandresidentsofltcfs/hcwinfluenzavaccineuptakereports/HPSC%20FluVax%20Uptake%20Report%202021-2022%20V1.3.pdf.
329. Public Health England. Seasonal influenza vaccine uptake in GP patients: winter season 2020 to 2021 - Final data for 1 September 2020 to 28 February 2021 [Internet]. London: PHE; 2021 [updated 2021 June; cited 2023 July 14]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/996033/Annual-Report_SeasonalFlu-Vaccine_GPs_2020_to_2021.pdf.
330. UK Health Security Agency. Seasonal influenza vaccine uptake in GP patients. Winter season 2021 to 2022 [Internet]. 2023 [updated 2023 January 10; cited 2023 July 14]. Available from: https://assets.publishing.service.gov.uk/media/64d0dd3d7a57080013144841/GP-patients-flu-annual-report-2021-to-2022-corrected_final.pdf.
331. UK Health Security Agency. Seasonal influenza vaccine uptake in GP patients. Winter season 2022 to 2023 [Internet]. London: UKHSA; 2023 [updated 2023 June; cited 2023 July 14]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1177042/GP-patients-flu-annual-report-2022-2023.pdf.
332. Health Protection Surveillance Centre. Healthcare Worker Seasonal Influenza Vaccine Uptake Reports [Internet]. Dublin: HPSC; 2023 [updated 2023 JUly 21; cited 2023 July 14]. Available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/surveillance/vaccineuptakeinhcwsandresidentsofltcfs/hcwinfluenzavaccineuptakereports/.
333. European Network for Health Technology Assessment. EUnetHTA Joint Action 2, Work Package 8 Deliverable. HTA Core Model® Version 3.0 [Internet]. EUnetHTA; 2016 [updated 2016; cited 2022 November 12]. Available from: https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf.
334. European Centre for Disease Prevention and Contol. Seasonal influenza

vaccines [Internet]. ECDC; 2023 [cited 2023 June 22]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/seasonal-influenza-vaccines.
335. European Centre for Disease Prevention and Contol. Seasonal Influenza Vaccination Strategies [Internet]. Stockholm: ECDC; 2023 [updated 2023 March 08; cited 2024 April 17]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/vaccination-strategies.
336. Evans MR, Prout H, Prior L, Tapper-Jones LM, Butler CC. A qualitative study of lay beliefs about influenza immunisation in older people. The British journal of general practice : the journal of the Royal College of General Practitioners. 2007;57(538):352-8.
337. Kan T, Zhang J. Factors influencing seasonal influenza vaccination behaviour among elderly people: a systematic review. Public health. 2018;156:67-78.
338. World Health Organization. How do vaccines work? [Internet]. Geneva: WHO; 2020 [updated 2020 December 08; cited 2023 July 14]. Available from: https://www.who.int/news-room/feature-stories/detail/how-do-vaccines-work.
339. Giubilini A. Vaccination ethics. British Medical Bulletin. 2020;137(1):4-12.
340. Biggerstaff M, Cauchemez S, Reed C, Gambhir M, Finelli L. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC infectious diseases. 2014;14(1):480.
341. European Centre for Disease Prevention and Contol. Seasonal influenza vaccination recommendations and coverage rates in EU/EEA Member States – An overview of vaccination recommendations for 2021-22 and coverage rates for the 2018–19 to 2020–21 influenza seasons. [Internet]. Stockholm: 2023; 2023 [updated 2023 October 09; cited 2024 April 18]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Seasonal-flu-vacc-recs-coverage-rates-EU-EEA.pdf.
342. Plans-Rubió P. The vaccination coverage required to establish herd immunity against influenza viruses. Preventive Medicine. 2012;55(1):72-7.
343. Kong G, Lim NA, Chin YH, Ng YPM, Amin Z. Effect of COVID-19 Pandemic on Influenza Vaccination Intention: A Meta-Analysis and Systematic Review. Vaccines. 2022;10(4).
344. Health Information and Quality Authority. Enhanced inactivated influenza vaccines for over 65s: Protocol for a health technology assessment [Internet]. Cork: HIQA; 2024 [updated 2024 January 25; cited 2024 April 30]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/enhanced-inactivated-influenza-vaccines-over.
345. Thomas RE. Is influenza-like illness a useful concept and an appropriate test of influenza vaccine effectiveness? Vaccine. 2014;32(19):2143-9.
346. Skou ST, Mair FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ, et al. Multimorbidity. Nature Reviews Disease Primers. 2022;8(1):48.
347. Centres for Disease Control and Prevention. People at Higher Risk of Flu Complications [Internet]. Atlanta: CDC; 2023 [updated 2023 August 25; cited 2024 April 30]. Available from: https://www.cdc.gov/flu/highrisk/index.htm#:~:text=Chronic%20lung%20disease%20(such%20as,Kidney%20diseases.

348. Gruneir A, Kwong JC, Campitelli MA, Newman A, Anderson GM, Rochon PA, et al. Influenza and seasonal patterns of hospital use by older adults in long-term care and community settings in Ontario, Canada. American journal of public health. 2014;104(2):e141-7.
349. Takayama M, Wetmore CM, Mokdad AH. Characteristics associated with the uptake of influenza vaccination among adults in the United States. Preventative Medicine. 2012;54(5):358-62.
350. Centers for Disease Contorl and Prevention. CDC Seasonal Flu Vaccine Effectiveness Studies [Internet]. Atlanta: CDC; 2024 [updated 2024 February 29; cited 2024 April 24]. Available from: https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm.
351. Welch VL, Metcalf T, Macey R, Markus K, Sears AJ, Enstone A, et al. Understanding the Barriers and Attitudes toward Influenza Vaccine Uptake in the Adult General Population: A Rapid Review. Vaccines [Internet]. 2023 2023/01//; 11(1):180. Available from: http://europepmc.org/abstract/MED/36680024.
352. Health Service Executive. Primary Care Reimbursement Service. List of Reimbursable Medicines [Internet]. Dublin: HSE; 2024 [cited 2024 March]. Available from: https://www.hse.ie/eng/staff/pcrs/items/.
353. Eurostat. EU statistics on income and living conditions (EU-SILC) [Internet]. Luxembourg: Eurostat; 2024 [cited 2024 May 28]. Available from: https://ec.europa.eu/eurostat/web/microdata/european-union-statistics-on-income-and-living-conditions#:~:text=EU-SILC%20data%20are%20used%20to%20monitor%20poverty%20and,EU-SILC%20data%2C%20make%20up%20the%20Joint%20Assessment%20Framework.
354. Revenue (Irish Tax and Customs). VAT Rates. Vaccines - Non-Oral [Internet]. Dublin: Office of the Revenue Commissioners; 2028 [updated 2018 August 04; cited 2024 May 28]. Available from: https://www.revenue.ie/en/vat/vat-rates/search-vat-rates/V/vaccines-nonoral.aspx.

Appendices

A4.1 AMSTAR 2 Quality Appraisal

AMSTAR 2 Questions		Primary Review 2020[10]		Updated Review 2024[138]	
		Yes / No	Comments	Yes / No	Comments
Q1	**Did the research questions and inclusion criteria for the review include the components of the PICO?**	Yes	Page 8, Table 2.1	Yes	Pages 9-10
Q2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**	Yes	"The proposed methodology for this systematic review was agreed with the EU/EEA National Immunisation Technical Group (NITAG) collaboration working group and subsequently submitted for registration on PROSPERO (registration pending)."	Yes	"The protocol for this systematic review and meta-analysis has been developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2020 statement. This review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) – CRD42023441114." The review methods match those listed in the protocol, with the exception of the sensitivity analyses that were outlined in the review but not listed in the protocol. Differences compared with the study protocol are listed in Appendix F.

Q3	**Did the review authors explain their selection of the study designs for inclusion in the review?**	Yes	Page 8, Section 2.2 Outlined in PICO but not explained	Yes	Page 9, Section 3.1 Randomised Controlled Trials (RCTs) and Non-Randomised Studies of Interventions (NRSI) with a control group were included. Selection of study designs is outlined but not explained by the review authors in the methods. Page 44. In the discussion the review authors explain the study design and inclusion criteria were tightened to overcome some methodological weaknesses in the primary review.
Q4	**Did the review authors use a comprehensive literature search strategy?**	Yes	Page 9, Section 2.3	Yes	Page 10 and Annex 1 The electronic databases MEDLINE and EMBASE were searched, with publication dates restricted to between 1 January 2020 and 24 July 2023. The complete search strategies are provided. Searches for ongoing and unpublished studies were performed in ClinicalTrials.gov. Supplementary searches were conducted. No language filters were applied.

Q5	**Did the review authors perform study selection in duplicate?**	Yes	Page 9, Section 2.4.1 Three reviewers independently reviewed the titles and available summaries of the remaining citations to identify those which warranted full-text review. The full texts were obtained and independently evaluated by two reviewers applying the defined eligibility criteria.	Yes	Page 11, Section 3.7.1 Title and abstracts were independently screened by two reviewers. Full texts were also independently checked for eligibility by two reviewers.
Q6	**Did the review authors perform data extraction in duplicate?**	Yes	Page 9, Section 2.4.2 Two reviewers then independently extracted data using the agreed data extraction form which was compared upon completion. Where disagreements occurred, discussions were held to reach consensus and where necessary, a third reviewer was involved.	Yes	Page 11, Section 3.7.2 Two pairs of review authors extracted the following study data and tabulated all the relevant information.
Q7	**Did the review authors provide a list of excluded studies and justify the exclusions?**	Yes	Appendix 3	Yes	Annex 2
Q8	**Did the review authors describe the included studies in adequate detail?**	Yes	Section 3 and Appendices 5-8	Yes	Section 4 and Tables 5-8
Q9	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in**	Yes	Page 10, Section 2.4.3 Cochrane Risk of Bias and ROBINS-I	Yes	Page 12 , Section 3.7.3 Cochrane Risk of Bias and ROBINS-I

	individual studies that were included in the review?				
Q10	**Did the review authors report on the sources of funding for the studies included in the review?**	No	The presence of industry funded studies included in risk of bias assessment, but not listed in table of characteristics of the included studies	Yes	Section 4 Tables 5 and 7 Sources of funding were listed in tables of characteristics for the included studies.
Q11	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**	Yes	Page 10 Meta-analysis plan explained	Yes	Page 12, Section 3.7.8 The meta-analysis explained, with deviations from protocol noted in Annex 6.
Q12	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	Yes	GRADE approach used	Yes	Page 13 Sensitivity analysis was planned excluding studies at high risk of bias for RCTS and serious of critical risk of bias for NRSIs. GRADE approach used
Q13	**Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?**	Yes	Section 4 GRADE approach was followed to consider certainty of evidence and the risk of bias was mentioned when advising a cautious interpretation of the results of this review.	Yes	Section 4 GRADE approach was followed to consider certainty of evidence and risk of bias was mentioned in discussion.

Q14	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**	Yes	Page 11 Assessment and investigation of heterogeneity explained. Section 4 GRADE approach was followed to consider certainty of evidence.	Yes	Section 3.7.7 Approach to assessment of heterogeneity explained in methods. Section 5 GRADE approach was followed to consider certainty of the evidence.
Q15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	Yes	Assessment of publication bias included in GRADE approach but not explicitly reported in the final report.	Yes	Annex 4 Funnel plot and visual inspection for small study effects was performed for outcomes with 10 or more studies. Section 5 GRADE approach was followed for primary effectiveness and safety outcomes, in which publication bias is one of five domains considered.
Q16	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**	Yes	No conflicts of interest were reported by any member of the evaluation team. This report was developed under contract NP/2019/OCS/10571 between the ECDC and HIQA.	Yes	No conflicts of interest were reported by any member of the review team. This report was funded by the EU4Health Programme under a service contract with the European Health and Digital Executive Agency (HaDEA).

					Grant: Service Contract HaDEA/OP/2021/0011
Q17	**Is the review peer-reviewed?**	Yes	Reviewed by HIQA and ECDC	Yes	Reviewed by ECDC
	Rating the overall confidence of the results of the review	**High**		**High**	

Key: AMSTAR – A Measurement Tool to Assess Systematic Reviews; ECDC – European Centre for Disease Prevention and Control; EEA – European Economic Area; EU – European Union; GRADE – Grading of Recommendations, Assessment, Development, and Evaluation; HaDEA – Health and Digital Executive Agency; HIQA – Health Information and Quality Authority; NITAG – National Immunisation Technical Group; NRSI – Non-randomised studies of intervention; PICO – Population, Intervention, Comparator and Outcomes; PRISMA-P – Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; PROSPERO – International Prospective Register of Systematic Reviews; RCT – Randomised controlled trial; RoB – Risk of bias; ROBINS-I – Risk Of Bias In Non-randomised Studies - of Interventions.

A5.1 Search strategies

Databases	Number of results	Date searched
Medline Complete via EBSCOhost	925	23/07/2023
Embase via Ovid	591	23/07/2023
CINAHL via EBSCOhost	116	23/07/2023
The Cochrane Library	259	23/07/2023
INAHTA database	4	
Total	1895	
Total after duplicates removed in Endnote and Covidence	**1442**	

Database Name	Medline Complete via Ebscohost

#	Query	Limiters/Expanders	Results
S17	S12 AND S16	Limiters - Date of Publication: 20200101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	925
S16	S13 OR S14 OR S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9,004,868
S15	TX (elder* or frail* or geriatric* or older OR "old age" OR aged OR ageing OR aging OR "over 65" OR >65 OR centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian or senior*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9,004,868
S14	(MH "Geriatrics+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	31,507
S13	(MH "Aged+") OR (MH "Aged, 80 and over+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,454,527
S12	S10 AND S11	Limiters - Date of Publication: 20130101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,868

S11	MH "Economics" OR MH "Models, Economic" OR MH "Costs and Cost Analysis+" OR MH "Economic Aspects of Illness" OR MH "Resource Allocation+" OR MH "Economic Value of Life" OR MH "Economics, Pharmaceutical" OR MH "Economics, Dental" OR MH "Fees and Charges+" OR MH "Budgets" OR MH "Decision Trees" OR TI budget* OR TI (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco-economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR TI (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR TI (value N2 (money OR monetary)) OR TI (markov OR monte carlo) OR TI (decision* N2 (tree* OR analy* OR model*)) OR AB budget* OR AB (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR AB (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR AB (value N2 (money OR monetary)) OR AB (markov OR monte carlo) OR AB (decision* N2 (tree* OR analy* OR model*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,961,950
S10	S3 AND S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	56,707
S9	S4 OR S5 OR S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	856,824
S8	TX (fluzone OR flublok OR fluad)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	977

S7	TX(HDTIV OR HD-TIV OR IIV3-HD OR HD-IIV3 OR QIVr OR HD-IIV4 OR RIV4 OR MF59 OR aTIV OR aQIV OR aIIV3)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,021
S6	AB (vaccin* OR inocula* OR immuni*)) OR TI (vaccin* OR inocula* OR immuni*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	795,035
S5	(MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	209,336
S4	(MH "Vaccination+") OR (MH "Influenza Vaccines")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	126,200
S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	155,183
S2	AB (flu OR influenza*) OR TI (flu OR influenza*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	146,855
S1	(MH "Influenza, Human") OR (MH "Influenza A virus+") OR (MH "Influenza B virus")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	82,384

Database Name	Embase via Ovid

#	Searches	Results
1	exp influenza/	106710
2	(flu or influenza*).ab,ti.	169686
3	1 or 2	195341
4	exp influenza vaccine/	44612
5	exp vaccination/	239206
6	exp immunization/	369205
7	(vaccin* or inocula* or immuni*).ab,ti.	919877
8	(HDTIV or HD-TIV or IIV3-HD or HD-IIV3 or QIVr or HD-IIV4 or RIV4 or MF59 or aTIV or aQIV or aIIV3).tw.	950

9	(fluzone or flublok or fluad).tw.	1228
10	4 or 5 or 6 or 7 or 8 or 9	1000170
11	3 and 10	75882
12	Economics/	244794
13	Cost/	62946
14	exp Health Economics/	1024932
15	Budget/	33426
16	budget*.ti,ab,kf.	47774
17	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	346451
18	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	530836
19	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	290659
20	(value adj2 (money or monetary)).ti,ab,kf.	4100
21	Statistical Model/	174309
22	economic model*.ab,kf.	6276
23	Probability/	144477
24	markov.ti,ab,kf.	38169
25	monte carlo method/	50664
26	monte carlo.ti,ab,kf.	63250
27	Decision Theory/	1839
28	Decision Tree/	21383
29	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	51559
30	or/12-29	2000483
31	11 and 30	8079

32	exp aged/	3611982
33	exp geriatrics/	41621
34	(elder* or frail* or geriatric* or older or "old age" or aged or ageing or aging or "over 65" or >65 or centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian* or senior*).tw.	2738780
35	32 or 33 or 34	5398454
36	31 and 35	3016
37	limit 36 to yr="2020 -Current"	717
38	limit 37 to conference abstracts	126
39	37 not 38	591

Database Name	CINAHL via EBSCOhost

#	Query	Limiters/Expanders	Last Run Via	Results
S17	S12 AND S16	Limiters - Published Date: 20200101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	116
S16	S13 OR S14 OR S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	2,237,060
S15	TX (elder* or frail* or geriatric* or older OR "old age" OR aged OR ageing OR aging OR "over 65" OR >65 OR centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian or senior*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	2,237,058
S14	(MH "Geriatrics+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	6,802
S13	(MH "Aged+") OR (MH "Aged, 80 and over+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	948,387
S12	S10 AND S11	Limiters - Published Date: 20130101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	695

S11	MH "Economics" OR MH "Costs and Cost Analysis+" OR MH "Economic Aspects of Illness" OR MH "Resource Allocation+" OR MH "Economic Value of Life" OR MH "Economics, Pharmaceutical" OR MH "Economics, Dental" OR MH "Fees and Charges+" OR MH "Budgets" OR MH "Decision Trees" OR TI budget* OR TI (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco-economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR TI (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR TI (value N2 (money OR monetary)) OR TI (markov OR monte carlo) OR TI (decision* N2 (tree* OR analy* OR model*)) OR AB budget* OR AB (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco-economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR AB (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR AB (value N2 (money OR monetary)) OR AB (markov OR monte carlo) OR AB	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	463,008

	(decision* N2 (tree* OR analy* OR model*))			
S10	S3 AND S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	14,845
S9	S4 OR S5 OR S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	108,664
S8	TX (fluzone OR flublok OR fluad)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	518
S7	TX(HDTIV OR HD-TIV OR IIV3-HD OR HD-IIV3 OR QIVr OR HD-IIV4 OR RIV4 OR MF59 OR aTIV OR aQIV OR aIIV3)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	571
S6	AB (vaccin* OR inocula* OR immuni*)) OR TI (vaccin* OR inocula* OR immuni*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	96,768
S5	(MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	33,038
S4	(MH "Influenza Vaccine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	10,905

S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	31,970
S2	AB (flu OR influenza*) OR TI (flu OR influenza*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	30,445
S1	(MH "Influenza, Human") OR (MH "Influenza A virus+") OR (MH "Influenza B virus")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	9,700

0

Database Name	The Cochrane Library

ID Search Hits
#1 MeSH descriptor: [Influenza, Human] explode all trees 3255
#2 MeSH descriptor: [Influenza B virus] explode all trees 321
#3 MeSH descriptor: [Influenza A virus] explode all trees 1021
#4 (flu OR influenza*):ti,ab,kw (Word variations have been searched) 12751
#5 #1 OR #2 OR #3 3482
#6 MeSH descriptor: [Vaccination] explode all trees 4014
#7 MeSH descriptor: [Immunization] explode all trees 6911
#8 MeSH descriptor: [Influenza Vaccines] explode all trees 1855
#9 (vaccin* OR inocula* OR immuni*):ti,ab,kw (Word variations have been searched) 40967
#10 (HDTIV OR HD-TIV OR QIVr OR RIV4 OR MF59 OR aTIV OR aQIV OR aIIV3):ti,ab,kw (Word variations have been searched) 416
#11 (fluzone OR flublok OR fluad):ti,ab,kw (Word variations have been searched) 221
#12 #6 OR #7 OR #8 OR #9 OR #10 OR #11 41183
#13 #5 AND #12 with Publication Year from 2020 to present, with Cochrane Library publication date from Jan 2020 to present, in Trials 357
#14 MeSH descriptor: [Aged] explode all trees 255415
#15 MeSH descriptor: [Geriatrics] explode all trees 400
#16 (elder* or frail* or geriatric* or older OR aged OR ageing OR "old age" OR aging OR "over 65" OR >65 OR centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian or senior*):ti,ab,kw (Word variations have been searched) 909597
#17 #14 OR #15 OR #16 909597
#18 #13 AND #17 with Publication Year from 2020 to present, with Cochrane Library publication date from Jan 2020 to present, in Trials 259

Database Name	INAHTA Database
Search strategies	Search 1: (influenza OR flu) AND (vaccine OR vaccination) FROM 2020 TO 2023 Search 2: "Influenza Vaccines"[mh]

A5.2 Data extraction tables for rapid review of economic modelling studies

General study characteristics	**Author name** **Year of publication** **DOI**	Alvarez 2023 10.1080/13696998.2023.2194193	
	Region or country	Belgium, Finland and Portugal	
	Type of economic evaluation	CUA and CEA	
	Population	≥65 years	
	Funding	Sanofi Pasteur	
Model characteristics	**Model type**	Static model with decision tree	
	Perspective	Belgium and Finland: Total payer (including patient co-payment) Portugal: National Health System (excluding co-payment)	
	Time horizon	Average influenza season (November to April), apart from premature deaths due to influenza, for which all QALYs lost up to life expectancy were captured.	
	Comparator	Standard QIV	
	Discount rates	No discounting for costs Country-specific discounting rate applied to premature death outcomes (Belgium: 1.5%; Finland: 3.0%; Portugal: 4.0%).	
	Sensitivity analysis	Deterministic and probabilistic	
Intervention strategy	**Dosing schedule**	1-dose	
	Vaccine type	HD-QIV	
	Age at vaccination	≥65 years	
	Coverage rate	Belgium: 53.1%; Finland: 49.5%; Portugal: 59.2%	
Model input parameters	**Efficacy/effectiveness**	Relative efficacy in preventing influenza cases of HD-QIV vs. standard QIV: 24.2% Relative efficacy in preventing influenza-related hospitalisation of HD-QIV vs. standard QIV:: 17.8% (Belgium, Portugal) and 24.3% (Finland) Standard QIV: efficacy against strain A (Belgium: 50.0%; Finland: 23.8%; Portugal: 46.0%) Standard QIV: efficacy against strain B (Belgium: 50.0%; Finland: 22.7%; Portugal: 46.0%)	
	Waning	NR	
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - Medication for ILI episode - GP visits (influenza-related) - ED visits (influenza-related) - hospitalisations (influenza-related) ▪ Vaccination costs - vaccine - administration of the vaccine	**Measurement and valuation** **Direct costs** ▪ Medical costs - overall cost for medication for ILI episode (reported separately for the three countries) - GP visit cost (reported separately for the three countries) - ED visit cost (reported separately for Belgium and Portugal; assumed to be included in cost of hospitalisation for Finland) - hospitalisation cost ([reported separately for the three countries] and by age group for Finland and Portugal) ▪ Vaccination costs - vaccine (by vaccine type and reported separately for the three countries) - administration of the vaccine (reported separately for Belgium and Finland; excluded for Portugal as considered a patient cost)
	Effects included	**Type of effects** **Direct effects** ▪ Influenza cases ▪ GP visits (influenza-related) ▪ ED visits (influenza-related) ▪ Hospitalisations (influenza-related) ▪ Hospitalisations (possibly influenza-related)	**Measurement and valuation** **Direct effects** ▪ Influenza attack rate (one rate applied to the three countries) ▪ Proportion of influenza cases for strain A (reported separately for each country) ▪ Probability of a GP visit (reported separately for each country) ▪ Probability of ED presentation conditional on influenza (reported separately for Belgium and Portugal; not applicable for Finland)

		- influenza broad definition - cardio-respiratory disease - respiratory disease - all-cause ▪ Mortality (influenza-related) ▪ All-cause mortality	▪ Hospitalisation rate/100,000 using ICD codes (reported separately for each country and by age group for Portugal) ▪ Relative efficacy in preventing influenza hospitalisation of HD-QIV versus standard QIV ▪ Probability of influenza-related death (reported separately for each country and by age group for Portugal) **QALYs** ▪ Baseline utility by gender and age group ▪ Utility loss per day of influenza (Belgium only) ▪ Utility loss per hospitalisation episode (Belgium only)
Economic results	**Type of summary ratio**	ICER (Incremental cost per QALY gained and increment cost per LY gained)	
	Overall payer perspective result	Belgium: HD-QIV ICER = €1,397/QALY gained versus standard QIV; HD-QIV ICER = €1,114/LY gained versus standard QIV Finland: HD-QIV ICER = €9,581/QALY gained versus standard QIV; HD-QIV ICER = €8,502/LY gained versus standard QIV Portugal: HD-QIV ICER = €15,267/QALY gained versus standard QIV; HD-QIV ICER = €9,634/LY gained versus standard QIV	
	Overall societal perspective result	N/A	
Authors conclusions	This study has shown that across several countries with different healthcare systems, switching from standard QIV to HD-QIV would contribute to significant improvement in terms of public health (lower number of flu cases, GP and ED visits, hospitalisations and deaths) while being a cost effective option.		

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; ED – emergency department; GP – general practitioner; HD-QIV – high-dose quadrivalent influenza vaccine; ICD – international classification of diseases; ICER – incremental cost effectiveness ratio; ILI – influenza-like illness; LY – life year; NR – not reported; QALY – quality-adjusted life year; QIV – standard-dose quadrivalent influenza vaccine.

General study characteristics	**Author name** **Year of publication** **DOI**	Bianculli, P.M 2022 10.1080/21645515.2022.2050653
	Region or country	Uruguay
	Type of economic evaluation	CUA
	Population	Children ≤4 years, adults ≥65 years, healthcare professionals, residents and staff in nursing homes, pregnant women, and individuals with >1 chronic medical condition that place them at risk.
	Funding	Sanofi Pasteur
Model characteristics	**Model type**	Decision-analytic static cost-effectiveness model
	Perspective	▪ Payer (estimated health costs directly associated with treating, managing, and caring for patients with influenza) ▪ Societal (indirect costs, specifically, loss of productivity due to influenza among the employed population, were also considered; premature deaths were not considered as a factor in the loss of productivity).
	Time horizon	Average influenza season, based on observed rates from 2013 to 2019 inclusive Costs and effects from premature mortality assessed over longer time horizon
	Comparator	TIV
	Discount rates	Not applicable to costs or effects within one year of vaccination 3% to LYs and QALYs lost due to premature influenza related death; DSA range: 0-6%;
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Dosing schedule**	1-dose
	Vaccine type	QIV
	Age at vaccination	Children ≤4 years, adults ≥65 years, healthcare professionals, residents and staff in nursing homes, pregnant women, and individuals with >1 chronic medical condition that place them at risk.
	Coverage rate	≤4 years: 23.0% 5–19 years (high-risk): 10.2% 20–49 years (high-risk): 10.2% 50–64 years (high-risk): 10.2% ≥65 years: 29.3%
Model input parameters	**Efficacy/effectiveness**	**Vaccine efficacy against A** ≤4 years: 0.59 [0.41-0.74] 5–19 years (high-risk): 0.61 [0.47-0.70] 20–49 years (high-risk): 0.61 [0.48-0.70] 50–64 years (high-risk): 0.51 [0.48-0.70] ≥65 years: 0.58 [0.38-0.72] **Vaccine efficacy against matched B** ≤4 years: 0.66 [0.12-0.94] 5–19 years (high-risk): 0.77 [0.17-0.94] 20–49 years (high-risk): 0.77 [0.18-0.94] 50–64 years (high-risk): 0.73 [0.18-0.96] ≥65 years: 0.69 [0.16-0.99] **Vaccine efficacy against mismatched B** ≤4 years: 0.44 5–19 years (high-risk): 0.52 20–49 years (high-risk): 0.52 50–64 years (high-risk): 0.49 ≥65 years: 0.47 **Cross-protection:** 67% [95% CI 54%–81%]
	Waning	NR

	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - GP visit (influenza-related) - Hospitalisation (influenza-related) - Prescribed drug cost ▪ Vaccination costs - vaccine **Indirect costs** ▪ Work days lost	**Measurement and valuation** **Direct costs** ▪ Medical costs - GP visit cost - Hospitalisation cost - Prescribed drug costs included those prescribed during a GP visit and those bought by the patient OTC reported separately for those aged ≤4 years and other age groups ▪ Vaccination costs - Cost of TIV and QIV reported separately. **Indirect costs** Calculated using human capital method ▪ Productivity losses, in workdays, due to illness reported separately for each age/risk group - ≤4 years - 5–19 years (high-risk) - 20–49 years (high-risk) - 50–64 years (high-risk) - ≥65 years ▪ Productivity losses due to death reported separately for each age/risk group - ≤4 years - 5–19 years (high-risk) - 20–49 years (high-risk) - 50–64 years (high-risk) - ≥65 years
	Effects included	**Type of effects** **Direct effects** ▪ Medical effects - Number of influenza cases avoided - GP visit (influenza-related) - Hospitalisation (influenza-related) - Mortality (influenza-related) - LYs gained	**Measurement and valuation** **Direct effects** ▪ Influenza attack rate – age and season specific Rate of influenza related GP consultations per 100,000 – age and season specific Rate of influenza related hospitalisations per 100,000 – age and season specific Rate of influenza related deaths per 100,000 – age and season specific Number of non-consulting cases per consulting case – age group specific **QALYs** ▪ Age specific baseline utility – weighted for prevalence of chronic conditions in Uruguay QALY losses due to influenza reported by age group - ≤4 years - 5–19 years (high-risk) - 20–49 years (high-risk) - 50–64 years (high-risk) - ≥65 years
Economic results	**Type of summary ratio**	ICER (Incremental cost per QALY gained)	

	Overall payer perspective result	ICER per QALY US$18,368. ICER ≤4 years $23,461 - 5–19 years (high-risk) $24,320 - 20–49 years (high-risk) $97,256 - 50–64 years (high-risk) $56,368 - ≥65 years $12,291
	Overall societal perspective result	ICER per QALY US$18,224. ICER ≤4 years $23,434 - 5–19 years (high-risk) $24,181 - 20–49 years (high-risk) $94,909 - 50–64 years (high-risk) $55,238 - ≥65 years $12,259
Authors conclusions	The findings from this health economic model indicate that in Uruguay, switching from TIV to QIV in the national influenza immunization program is likely to be cost effective in the eligible populations overall due to predicted reductions in influenza-related consultations, hospitalizations, and deaths. Probabilistic sensitivity analysis confirmed that switching from TIV to QIV would be cost effective for 50% of simulations at a WTP per QALY gained of US$20,000.	

Key: CI – confidence interval; CUA – cost-utility analysis; DSA – deterministic sensitivity analysis; GP – general practitioner; ICER – incremental cost-effectiveness ratio; LY – life year; NR – not reported; OTC – over-the-counter; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccines; TIV – trivalent influenza vaccine; WTP – willingness-to-pay.

General study characteristics	**Author name,** **Year of publication** **DOI**	Choi MJ 2022 10.3390/vaccines10030445
	Region or country	South Korea
	Type of economic evaluation	CUA
	Population	19–64 years (at risk adults) 50–64 years (adults) ≥65 years (older adults)
	Funding	Government funded by the Korea Disease Control and Prevention Agency, grant number 2018P241001.
Model characteristics	**Model type**	Static decision-tree model
	Perspective	▪ Societal perspective ▪ Healthcare sector perspective (only in adults aged 50-64 years and at-risk adults aged 19-64 years)
	Time horizon	One year
	Comparator	**Older adults aged ≥65 years** ▪ Program 1 (baseline): all older adults received the TIV according to the current Korean NIP. **Adults aged 50–64 years and at-risk adults aged 19–64 years** ▪ Program 1 (baseline): individuals receiving influenza vaccination with out-of-pocket expenses (TIV or QIV).
	Discount rates	Given that the model compared only cohorts over one year, discounting was not applied to either cost or outcomes; only productivity loss due to early death from influenza was discounted at 4.5% in accordance with the literature.
	Sensitivity analysis	Deterministic one-way sensitivity analysis and probability sensitivity analysis, Scenario analysis - discount rate, community effect
Intervention strategy	**Dosing schedule**	1-dose
	Vaccine type	**Older adults aged ≥65 years** ▪ Programs 2, 3, and 4: assume the introduction of a QIV, aTIV or HD-QIV to the NIP instead of the TIV, and target a vaccination rate of 85%. **Adults aged 50–64 years and at-risk adults aged 19–64 years** ▪ Programs 2 and 3: assume the introduction of a TIV and QIV, respectively, into the NIP with a target vaccination rate of 80%.
	Age at vaccination	19–64 years (at-risk adults) 50–64 years (adults) ≥65 years (older adults)
	Coverage rate	**Baseline program coverage** ▪ 35.8% (at-risk adults aged 19–64 years) ▪ 41.4% (adults aged 50–64 years) ▪ 85% (older adults aged ≥65 years) **Extended program coverage** ▪ 80% (adult groups) ▪ 85% (older adults)
Model input parameters	**Efficacy/effectiveness**	**19–49 years (at-risk adults)** ▪ TIV: 59% ▪ QIV: 64.2% (59–70.3%) **50–64 years (at-risk adults)** ▪ TIV: 59% ▪ QIV: 64.2% (59–70.3%) **50–64 years** ▪ TIV: 59% ▪ QIV: 64.2% (59–70.3%)

		≥65 years ▪ TIV: 58% ▪ QIV: 63.2% (58–69.3%) ▪ aTIV: 66.4% (62.2–74.8%) ▪ HD-QIV: 72.0% (68.1–76.7%)	
	Waning	NR	
	Costs included	**<u>Type of cost</u>** **Direct costs** Direct medical per case - Uncomplicated outpatient - Complicated outpatient - Uncomplicated hospitalisation - Complicated hospitalisation Direct non-medical - Nursing - Transportation costs Vaccine related cost - Vaccine acquisition - Vaccine administration **Indirect costs** ▪ Productivity losses due to illness Productivity losses due to premature death	**<u>Measurement and valuation</u>** **Direct costs** Probability of influenza – age group stratified Probability of complicated flu – age group stratified ▪ Outpatient costs – age group stratified - Cost of office and ED visits (within 14 days of initial visit) - Prescription drugs at time of visit (only oseltamivir in uncomplicated cases) - Influenza rapid antigen test costs - Number of visits – age group stratified: uncomplicated/complicated Hospitalisation costs – age group stratified - Probability of hospitalisation conditional on flu - Inpatient stay – age group specific - Outpatient visits - Prescription drugs within 14 days of diagnosis - Length of stay – age group stratified, uncomplicated/complicated Nursing costs – age group stratified - Cost of daily nursing care - Probability of hospitalised patient receiving daily nursing care - Duration of care – outpatient (number of visits) inpatient (LOS) – age group specific Transportation costs per case of hospitalisation or outpatient visit Vaccine costs - Cost of vaccines – vaccine specific, age group specific, including administration - Out-of-pocket expenses used in reference case for non-target populations **Indirect costs** Human capital approach to estimating indirect costs based on workdays lost ▪ Workdays lost in visiting clinics (number of outpatient visits) Workdays lost during hospitalisation (LOS) Cost of lost income due to early death – discounted - Age specific average yearly income - Age specific life expectancy Probability of death conditional on influenza - Age specific average yearly income - Age specific life expectancy - Probability of death conditional on influenza

	Effects included	**Type of effects** **Direct effects** ▪ Influenza cases ▪ Hospitalisations ▪ Complications ▪ Deaths	**Measurement and valuation** **Direct effects** ▪ Probability of influenza – age group stratified Probability of complicated flu – age group stratified Probability of hospitalisation – age group stratified Probability of death conditional on influenza – age groups stratified **QALY loss per case** ▪ Utility (at-risk adults aged 19–64 years, adults aged 50–64 years and older adults aged ≥65 years) - Baseline utility - Uncomplicated outpatient disutility - Complicated outpatient disutility - Uncomplicated hospitalisation disutility - Complicated hospitalisation disutility - Duration of disutility (number of outpatient visits/length of inpatient stay)
Economic results	**Type of summary ratio**	ICER per QALY	
	Overall healthcare perspective result	**19–64 years (at-risk adults)** ▪ TIV: ICER = $23,020/QALY ▪ QIV: ICER = $53,050/QALY **50–64 years** ▪ TIV: ICER = $37,352/QALY ▪ QIV: ICER = $86,463/QALY	
	Overall societal perspective result	**19–64 years (at-risk adults)** ▪ TIV: cost saving ▪ QIV: cost saving **50–64 years** ▪ TIV: cost saving ▪ QIV: ICER = $3,661/QALY **≥65 years** ▪ QIV: ICER = $46,486/QALY ▪ aTIV: ICER = $34,314/QALY ▪ HD-QIV: cost saving	
Authors conclusions	In conclusion, the introduction of the influenza vaccine NIP (TIV or QIV) is expected to be cost effective in the expanded adult age group (aged 50–64 years) and the at-risk group (aged 19–64 years). Moreover, this study indicates that highly immunogenic vaccines for older adults are likely to be favoured over the standard non-adjuvanted vaccine, based on currently available data. The relative cost effectiveness of such formulations (aTIV and HD-QIV) should be re-evaluated after establishing their effectiveness and the Korean price.		

Key: aTIV – adjuvanted trivalent influenza vaccine; CUA – cost-utility analysis; ED – emergency department; HD-QIV – high-dose quadrivalent influenza vaccine; ICER – incremental cost-effectiveness ratio; LOS – length of stay; NIP – National Immunization Programme; NR – not reported; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccine; TIV – trivalent influenza vaccine.

General study characteristics	**Author name** **Year of publication** **DOI**	Crepey 2020 10.1371/journal.pone.0233526
	Region or country	Spain
	Type of economic evaluation	CUA
	Population	<65 years (high-risk) and ≥65 years
	Funding	Sanofi Pasteur
Model characteristics	**Model type**	Dynamic transmission model and decision-tree model
	Perspective	Public healthcare system payer and societal perspective
	Time horizon	Not clear
	Comparator	TIV
	Discount rates	3%
	Sensitivity analysis	Deterministic univariate and probabilistic multivariate sensitivity analyses
Intervention strategy	**Dosing schedule**	1-dose
	Vaccine type (intervention)	QIV
	Age at vaccination	<65 years (high-risk) and ≥65 years
	Coverage rate	0–4 years: 1.68% 5–14 years: 1.68% 15–44 years: 5.22% 45–64 years: 15.67% ≥65 years: 58.16%
Model input parameters	**Efficacy/effectiveness**	**AH1N1** 0–0.5 years: 0 0.5–5 years: 0.5085 5–10 years: 0.473 10–15 years: 0.41 15–20 years: 0.41 20–40 years: 0.4165 40–60 years: 0.6665 60–100 years: 0.5 **AH3N2** 0–0.5 years: 0 0.5–5 years: 0.5085 5–10 years: 0.473 10–15 years: 0.41 15–20 years: 0.41 20–40 years: 0.4165 40–60 years: 0.6665 60–100 years: 0.5 **B Victoria** 0–0.5 years: 0 0.5–5 years: 0.6102 5–10 years: 0.5676 10–15 years: 0.492 15–20 years: 0.492 20–40 years: 0.4998 40–60 years: 0.7998 60–100 years: 0.6

		B Yamagata 0–0.5 years: 0 0.5–5 years: 0.6102 5–10 years: 0.5676 10–15 years: 0.492 15–20 years: 0.492 20–40 years: 0.4998 40–60 years: 0.7998 60–100 years: 0.6 Vaccine cross-protection ratio (B strains): 70%	
	Waning	NR	
	Costs included	**<u>Type of cost</u>** **Direct costs** ▪ Medical - Outpatient visit without complication - Outpatient visit otitis media - Outpatient visit pneumonia or other complications - Hospitalisation - Medical cost per death - Medication ▪ Vaccine - Vaccine price **Indirect costs** ▪ Productivity losses - Lost workdays: Outpatient visit - Lost workdays: Hospitalisation - Daily earnings for productivity losses	**<u>Measurement and valuation</u>** **Direct costs** ▪ Medical - Outpatient visit without complication – one cost reported for all age groups. - Outpatient visit otitis media – one cost reported for all those aged 0-14 years. - Outpatient visit pneumonia or other complications – one cost reported for all those aged 0-14 years. - Hospitalisation – costs reported separately for each of the following age groups 0–4 years, 5–14 years, 15–44 years, 45–64 years, ≥65 years. - Medical cost per death – costs reported separately for each of the following age groups 0–4 years, 5–14 years, 15–44 years, 45–64 years, ≥65 years. - Medication – one cost reported for all age groups. ▪ Vaccine - Vaccine price reported separately for TIV and QIV. No administration costs included in the analysis as these are assumed to be the same across both vaccines. **Indirect costs** ▪ Productivity losses (Days of productivity loss due to outpatient visit or hospitalisation were only assigned to adults (≥18 years). - Lost workdays for outpatient visit reported separately for those aged 15-44 years and 45-64 years. - Lost workdays for hospitalisation reported separately for those aged 15-44 years and 45-64 years. - Daily earnings for productivity losses reported separately for those aged 15-44 years and 45-64 years.
	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Medical - Cases - Outpatient visit without complication - Outpatient visit with otitis media - Outpatient visit with pneumonia or other complications	**<u>Measurement and valuation</u>** **Direct effects** ▪ The epidemiological model produced weekly symptomatic influenza incidence, incidence per age group and per season, number of influenza cases per subtype and lineage for all years of the study period.

		- Hospitalisation - Death	▪ Probability of outpatient visit without complication reported separately for the following age groups: 0–1 years, 2–4 years, 5–14 years, 15–19 years, 20–49 years, 50–64 years, 65–69 years, 70–74 years, 75–79 years, ≥80 years. ▪ Probability of outpatient visit with otitis media reported separately for the following age groups: 0-6 months, 6-59 months, 5-9 years, 10-14 years. ▪ Probability of outpatient visit with pneumonia or other complications reported separately for the following age groups: 0-6 months, 6-59 months, 5-9 years, 10-14 years. ▪ Probability of hospitalisation reported separately for the following age groups: 0–1 years, 2–4 years, 5–14 years, 15–19 years, 20–49 years, 50–64 years, 65–69 years, 70–74 years, 75–79 years, ≥80 years. ▪ Probability of death reported separately for the following age groups: 0–1 years, 2–4 years, 5–14 years, 15–19 years, 20–49 years, 50–64 years, 65–69 years, 70–74 years, 75–79 years, ≥80 years. Life expectancy reported according to the following age groups: 0–4 years, 5–14 years, 15–44 years, 45–64 years, ≥65 years. **QALY loss per case** Baseline healthy utility – age group stratified ▪ QALY loss per inpatient influenza episode reported separately for those aged 0–18 years, 19–49 years, 50–64 years, ≥65 years. ▪ QALY loss per outpatient influenza episode reported separately for those aged 0–18 years, 19–49 years, 50–64 years, ≥65 years.
Economic results	**Type of summary ratio**	ICER per QALY	
	Overall payer perspective result	ICER = €2,751 per QALY gained	
	Overall societal perspective result	ICER = €1,527 per QALY gained	
Authors conclusions	Using a dynamic model as recommended by most recent vaccine evaluation guidelines, our study shows that QIV could be an efficient intervention for the National Health Service (from a payer perspective), being even more efficient from a societal perspective. This analysis also shows that most health benefits of QIV are obtained replacing TIV in the ≥65-year-old population.		

Key: CUA – cost-utility analysis; ICER – incremental cost-effectiveness ratio; NR – not reported; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccine; TIV – trivalent influenza vaccine.

General study characteristics	**Author name** **Year of publication** **DOI**	Fochesato 2022 10.3390/vaccines10081360	
	Region or country	Spain	
	Type of economic evaluation	CUA	
	Population	≥65 years	
	Funding	Seqirus USA Inc.	
Model characteristics	**Model type**	Dynamic transmission model and decision tree Cycle length not specified	
	Perspective	Public healthcare system payer and societal	
	Time horizon	Not clear	
	Comparator	Standard QIV	
	Discount rates	Not applicable to costs and effects in the year of vaccination. 3% for QALYs accrued after the first year and indirect costs associated with averted deaths	
	Sensitivity analysis	One-way deterministic sensitivity and probabilistic sensitivity analysis	
Intervention strategy	**Dosing schedule**	1-dose	
	Vaccine type (intervention)	aQIV	
	Age at vaccination	≥65 years	
	Coverage rate	0–4 years: 4.55% 5–17 years: 5.18% 18–49 years: 2.91% 50–64 years: 15.66% 65–69 years: 59.84% 70–74 years: 67.41% 75–79 years: 68.36% 80–84 years: 76.39% ≥85 years: 72.23% (Unclear if under 65's coverage rate here is high risk as reports also coverage in this age group is 0%)	
Model input parameters	**Efficacy/effectiveness**	Standard QIV absolute vaccine effectiveness 0.5-1 H1N1 69% H3N2 43% B 66.5% 2-6 H1N1 69% H3N2 43% B 66.5% 7-17 H1N1 73% H3N2 35% B 77% 18-64 H1N1 73% H3N2 35% B 77% 65+ H1N1 62% H3N2 24% B 52.1% aQIV relative vaccine effectiveness 34.6% – laboratory confirmed influenza 13.9% – including ILI outcomes for flu related medical encounters +/- pneumonia in various clinical settings	
	Waning	NR	
	Costs included	**Type of cost** **Direct costs** Cost of flu without complications Cost of flu with ambulatory complications Cost of hospitalisation **Vaccine related costs** Vaccine acquisition cost Vaccine administration cost **Indirect costs**	**Measurement and valuation** **Direct costs** Cost of flu without complications - Cost of GP visit (ambulatory/home visit) - Cost of pharmaceuticals (antivirals, symptom relief, antibiotics) - Cost of ED visit Probability of GP visit- age group stratified - Probability of GP ambulatory visit – age group stratified - Probability of GP home visit – age group stratified Probability of ED visit – age group stratified

		Productivity loss due to influenza Productivity loss due to premature death	Cost and probability of Flu with ambulatory complications in 0-17 - URTI - LRTI Cost and probability of Flu with ambulatory complications in 18+ - Antibiotic treatment - Specialist visit - X-ray thorax - X-ray sinus - X-ray other - Haematology - ECG - Blood analysis - Throat swab - Audiometry Cost of hospitalisation by complication - URTI - Pneumonia - COPD - Bronchitis - Cardiac Probability of hospitalisation – age group stratified - Probability of hospitalisation due to URTI (by age group) - Probability of hospitalisation due to bronchitis (by age group) - Probability of hospitalisation due to pneumonia without complications (by age group) - Probability of hospitalisation due to pneumonia with complications (by age group) - Probability of hospitalisation due to COPD (by age group) - Probability of hospitalisation due to cardiac concerns (by age group) **Vaccine related costs** Cost of standard QIV per dose in Euro Cost of aQIV per dose in Euro Vaccine administration cost in Euro **Indirect costs** Friction cost method Number of working hours per week Average wages per hour Employment rate Average number of working days lost for cases that did not require hospitalisation Average number of working days lost for hospitalisation Probability of patients staying home as a result of developing flu symptoms Probability of parents having to take care of sick children

	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Symptomatic cases ▪ Flu requiring medical care without complications ▪ Flu requiring medical care with complications ▪ Flu requiring hospitalisation ▪ Mortality	**<u>Measurement and valuation</u>** **Direct effects** ▪ Number of influenza cases by season ▪ Probability of GP visit – age group stratified - Probability of GP ambulatory visit – age group stratified - Probability of GP home visit – age group stratified ▪ Probability of ED visit – age group stratified ▪ Probability of influenza related complications – age group stratified - Probability of UTRI - Probability of bronchitis - Probability of pneumonia - Probability of other respiratory complications ▪ Probability of hospitalisation – age group stratified - Probability of hospitalisation due to URTI (by age group) - Probability of hospitalisation due to bronchitis (by age group) - Probability of hospitalisation due to pneumonia without complications (by age group) - Probability of hospitalisation due to pneumonia with complications (by age group) - Probability of hospitalisation due to COPD (by age group) - Probability of hospitalisation due to cardiac concerns (by age group) ▪ Risk of influenza related mortality – age group stratified **QALY loss per case** ▪ Baseline healthy utility – age group stratified ▪ Disutility of influenza symptoms without medical visit ▪ Disutility of influenza symptoms with medical visit ▪ Disutility of influenza symptoms with complications ▪ Disutility of influenza symptoms with complications and hospitalisation
Economic results	**Type of summary ratio**	ICER per QALY gained	
	Overall payer perspective result	ICER = €2,240 per QALY gained at rVE 34.6% ICER = €6,694 per QALY gained at rVE 13.9%	
	Overall societal perspective result	aQIV was cost saving compared with standard QIV at rVE 34.6% ICER = €3,936 per QALY gained at rVE 13.9%	
Authors conclusions	Results for the analysis have shown that aQIV represents an affordable and highly cost-effective alternative to vaccinate the adults aged ≥65 years and older in Spain. Results from these analyses should help inform regional decision-makers in Spain as they determine which vaccination strategies should be funded that will provide the highest health outcomes for the older adult population.		

Key: aQIV – adjuvanted quadrivalent influenza vaccine; COPD – chronic obstructive respiratory diseases; CUA – cost-utility analysis; ECG – electrocardiogram; ED – emergency department; GP – general practitioner; ICER – incremental cost-effectiveness ratio; ILI – influenza like illness; LRTI – lower respiratory tract infection; NR – not reported; QALY – quality-adjusted life year; QIV – quadrivalent influenza vaccine; rVE – relative vaccine effectiveness; Standard QIV – standard quadrivalent influenza vaccine; URTI – upper respiratory tract infection.

General study characteristics	**Author Name, Year of Publication, DOI**	Jacob 2023 10.3390/vaccines11040753	
	Region, Country	Denmark, Norway and Sweden	
	Type of Economic Evaluation	CUA	
	Population	≥65 years (modelled populations were further divided into two subgroups (65-74 years and ≥75 years)	
	Funding	Seqirus	
Model characteristics	**Model type**	Static Decision Tree	
	Perspective	Healthcare and societal	
	Time horizon	One influenza season (assumed to last 6 months)	
	Comparator	Standard QIV (strategy 2) HD-QIV (strategy 3)	
	Discount rates	Country-specific discount rates for health and cost outcomes Denmark: 3.5% Norway: 4.0% Sweden: 3.0%	
	Sensitivity analysis	Attack rate: 7.2% (among unvaccinated population), 5% and 10% tested in sensitivity analysis. Scenario analyses were conducted to evaluate the robustness of the model results by changing input parameters and or assumptions using alternative data sources and hypotheses. Univariate DSA was conducted using available 95% CIs for model parameters, or a ±20% variation around the base case value. The joint uncertainty of the model was assessed in PSA using second-order Monte Carlo simulations (1000 iterations).	
Intervention strategy	**Dosing schedule**	1-dose	
	Vaccine type	aQIV (strategy 1)	
	Age at vaccination	≥65 years (modelled populations were further divided into two subgroups (65-74 years and ≥75 years)	
	Coverage rate	Vaccine coverage rates were assumed to be the same for the three strategies and varied by country. Non-vaccinated patients (i.e. 100% coverage rate) were included in the 'No vaccine' arm of the model. Denmark: 75.0% Norway: 59.7% Sweden: 60.0%	
Model input parameters	**Efficacy/effectiveness**	rVE HD-QIV vs standard QIV: 24.2% rVE aQIV vs HD-QIV: 3.2% Standard QIV VE against Influenza A H1N1: 62.0% Standard QIV VE against Influenza A H3N2: 24.0% Standard QIV VE against influenza B: 63.0%	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ Vaccination - Vaccine - Administration ▪ Medical costs - GP visit - Hospitalisation (influenza-related complications*) - Outpatient (influenza-related complications*) **Indirect costs** - Productivity loss - Non-prescription medication - Transportation	**Measurement and valuation** **Direct costs** Vaccination - Vaccine cost (standard QIV, HD-QIV and aQIV) reported separately for each country in € - aQIV cost presented as a ratio vs standard QIV - Administration cost reported separately for each country in € Medical costs - GP visit reported separately for each country - Hospitalisation (influenza-related complications*) reported separately for each country - Outpatient (influenza-related complications*) reported separately for each country

			Indirect costs - Proportion of the population employed (aged 65-74 years) and the labour costs per day (€) reported separately for each country - Non-prescription medication costs reported separately for each country - Transportation costs for vaccination, outpatient and hospitalisation reported separately for each country
	Effects included	**<u>Type of effects</u>** **Direct effects** - Number of symptomatic influenza - Number of GP visits - Number of influenza-related complications* - Number of hospitalisations - Number of deaths **Indirect effects** - Number of days lost due to symptomatic influenza - Number of days lost due to hospitalisation	**<u>Measurement and valuation</u>** **Direct effects** - Probability of developing symptomatic influenza taken from literature (single value reported for all countries) - Probability of medical attention (GP visit) taken from literature (single value reported for all countries) - Probability of developing influenza-related complications* (single value reported for all countries) – stroke stratified for those aged 65-74 years and those aged ≥75 years - Probability of hospitalisation due to influenza-related complications* (single value reported for all countries) – pneumonia, myocarditis and HF stratified for those aged 65-74 years and those aged ≥75 years - Death due to influenza-related complications* (single value reported for all countries) – renal complications, MI and HF stratified for those aged 65-74 years and those aged ≥75 years **Indirect effects** - Number of days lost due to symptomatic influenza (single value reported for all countries) - Number of days lost due to hospitalisation (single value reported for all countries) reported separately for each influenza-related complication* **QALY** ▪ Baseline utilities reported separately for those aged 65-69 years 70-74 years and ≥75 years ▪ Utility decrements - Symptomatic influenza (single value reported for all countries) - Hospitalisation due to influenza-related complications* (single value reported for all countries) reported separately for each influenza-related complication - Outpatient with influenza-related complications* (single value reported for all countries) reported separately for each influenza-related complication - Life years - QALYs
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	▪ aQIV versus standard QIV - Denmark - €10,170/QALY - Norway - €12,515/QALY - Sweden - €9,894/QALY ▪ aQIV versus HD-QIV - Denmark - Dominant	

		- Norway - Dominant - Sweden - Dominant
	Overall societal perspective result	▪ aQIV versus standard QIV - Denmark - €5,472/QALY - Norway - €7,906/QALY - Sweden - €4,856/QALY ▪ aQIV versus HD-QIV - Denmark - Dominant - Norway - Dominant - Sweden - Dominant
Authors conclusions	Analyses indicated that, in an average influenza season, aQIV may be a cost-effective strategy compared to standard QIV and may be cost saving when compared to HD-QIV for preventing seasonal influenza among adults aged ≥65 years in Denmark, Norway, and Sweden. The introduction of aQIV may prevent a significant number of influenza cases and influenza-related complications, leading to a lower disease burden for patients and reducing the economic burden for healthcare payers and society.	

Key: aQIV – adjuvanted quadrivalent influenza vaccine; CI – confidence interval; CUA – cost-utility analysis; DSA – deterministic sensitivity analysis; GP – general practitioner; HD-QIV – high-dose quadrivalent influenza vaccine; HF – heart failure; ICER – incremental cost-effectiveness ratio; MI – myocardial infarction; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; rVE – relative vaccine effectiveness; standard QIV – standard-dose quadrivalent influenza vaccine; VE – vaccine effectiveness.
*Influenza-related complications included bronchitis, pneumonia, URTI – upper respiratory tract infection, myocardial infarction, renal complications, CNS – central nervous system (complications), GI – gastro intestinal (bleeding), myocarditis, heart failure and stroke.

General study characteristics	**Author name** **Year of publication** **DOI**	Kim De Luca, 2023 10.1016/j.vaccine.2023.04.069	
	Region or country	US	
	Type of economic evaluation	CUA	
	Population	US population aged >6 months Cohorts were stratified by age: 6–23 months, 2–4 years, 5–11 years, 12–17 years, 18–49 years, 50–64 years, and ≥65 years. Each age group was further stratified by risk status: those at higher risk for influenza-related complications ("high-risk") or not ("non-high-risk"). Individuals aged ≥65 years were all assumed to be at higher risk for influenza related complications.	
	Funding	Centers for Disease Control and Prevention	
Model characteristics	**Model type**	State transition simulation model Six health states: uncomplicated influenza, medically attended influenza, influenza related hospitalisation, influenza related death, no influenza related health events. Cycle length not specified	
	Perspective	Societal (base-case analysis) and healthcare sector perspectives (scenario analysis)	
	Time horizon	One year (permanent outcomes, i.e. death and long-term sequelae, were included for a lifetime duration).	
	Comparator	No vaccination.	
	Discount rates	No discount rate accrued to costs and effects in vaccination year. The discount rate for the base-case analysis was 3% for costs and QALYs associated with permanent outcomes (i.e. death and long-term sequelae).	
	Sensitivity analysis	Deterministic one way sensitivity analysis, PSA, Scenario analyses: perspective, vaccination setting, exclude time costs, alternate vaccine effectiveness, added productivity losses as additional cost, threshold analysis of probability of influenza.	
Intervention strategy	**Dosing schedule**	Children received 2 doses	
	Vaccine type (intervention)	▪ Base case: any vaccine ▪ Scenarios - Strategy 2- RIV4 age ≥18 years - Strategy 3- HD-IIV4 age ≥65 years - Strategy 4- aIIV4 age ≥65 years	
	Age at vaccination	See population	
	Coverage rate	Not specified	
Model input parameters	**Efficacy/effectiveness**	6 months–23 months: 0.46 2-4 years: 0.46 5-11 years: 0.44 12-17 years: 0.42 18-49 years: 0.35 50-64 years: 0.40 ≥65 years: 0.27	
	Waning	Not applicable	
	Costs included	**Type of cost** ▪ **Direct costs** - Medications - Physician visits - Hospitalisations - Other health services - Special education costs related to long term sequelea due to influenza related hospitalisations	**Measurement and valuation** ▪ **Direct costs** - Cost of OTC medications for uncomplicated influenza in USD (age group stratified) - Cost of Outpatients visit for influenza in USD (age group stratified, HR, NHR) - Probability of an outpatient visit given influenza illness (age group stratified, HR, NHR) - Cost of Hospitalisation in USD (age group stratified, HR, NHR)

		▪ **Vaccine related costs** - Vaccine acquisition costs - Vaccine administration costs - Special education costs related to long term sequelea due to vaccination related events - Vaccine specific medical visits ▪ **Indirect costs** - Parent or adult recipient time costs for vaccination ▪ Scenario - Productivity losses due to influenza or vaccine related illness - Productivity loss of earnings	- Probability of and Incidence of influenza-attributable hospitalisations, per 100,000 (age group stratified, HR, NHR) - Cost of long-term sequelae following influenza related hospitalisation (age group stratified <18 years only) - Probability of long-term sequelae after hospitalisation (children only) ▪ **Vaccine related costs** - Cost of IIV4 per dose (age group stratified) - Cost of RIV4 per dose (≥18 years) - Cost of HD-IIV4 per dose (≥65 years) - Cost of aIIV4 per dose (≥65 years) - Cost of administration - Physician office setting existing visit - Physician office setting additional visit - Mass vaccination clinic - Probability of first time vaccination (age group stratified <4 years) - Probability of one extra visit to receive vaccine (age group stratified) - Probability of two extra visits to receive vaccine (age group stratified <4 years) - Probability of mass vaccination (age group stratified ≥18 years, HR, NHR) - Cost of physician visit for injection site reaction (<18 years) - Cost of physician visit for systemic reaction (age group stratified, HR, NHR) - Medical costs of anaphylaxis- vaccine related (age group stratified) - Medical costs of Guillain-Barré syndrome (age group stratified) - Costs of long-term sequelae due to Guillain-Barré syndrome (age group stratified) - Probability of injection site reaction (age group stratified) - Probability of outpatient visit given injection site reaction (age group stratified) - Probability of systemic reaction (HR, NHR) - Probability of outpatient visit given systemic reaction (age group stratified, HR, NHR) - Probability of anaphylaxis (age group stratified) - Probability of death from anaphylaxis (<18 years) - Probability of Guillain-Barré syndrome (age group stratified) - Probability of death from Guillain-Barré syndrome (<18 years) - Probability of long-term sequelae after Guillain-Barré syndrome (<18 years) ▪ **Indirect costs** - Parent time in hours (for child vaccination) - Hourly earnings for parent/adult - Recipient time in hours - Physician office setting existing visit - Physician office setting additional visit

			- Mass vaccination clinic ▪ Scenario: - Productivity losses in days - Influenza, non-medically attended (18-49 years) - Influenza, medically attended (18-49 years) - Influenza related hospitalisation (18-49 years, HR, NHR) - Systemic reaction (18-49 years) - Anaphylaxis (18-49 years) - Guillain-Barré syndrome (18-49 years) - Productivity losses, lost earnings - Daily productivity (18-49 years) - Influenza related death (18-49 years)
	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Episodes of influenza illness - Medically attended - Non-medically attended ▪ Influenza related hospitalisation - Without long-term sequelae - With long-term sequelae ▪ Influenza related death ▪ Vaccine related adverse events **Indirect effects** ▪ Indirect effects of reduced transmission were not included in this study because assumptions about the effectiveness of vaccines to reduce transmission are uncertain for seasonal influenza	**<u>Measurement and valuation</u>** **Direct effects** - Probability of influenza illness (AR) (age group stratified) - Probability of an outpatient visit given influenza illness (age group stratified, HR, NHR) - Probability of and Incidence of influenza-attributable hospitalisations, per 100,000 (age group stratified, HR, NHR) - Probability of and incidence of influenza-attributable deaths, per 100,000 (age group stratified, HR, NHR) - Probability of injection site reaction (age group stratified) Probability of outpatient visit given injection site reaction (age group stratified) - Probability of systemic reaction (HR, NHR) - Probability of anaphylaxis (age group stratified) - Probability of death from anaphylaxis (<18 years) - Probability of Guillain-Barré syndrome (age group stratified) - Probability of death from Guillain-Barré syndrome (<18 years) - Probability of long-term sequelae after Guillain-Barré syndrome (<18 years) **QALY Loss** ▪ Base case of 18-49 years (in most cases) multiple by age weights for other age groups. - Duration of symptoms for each - Disutility associated with influenza illness - Disutility associated with hospitalisation - Disutility associated with a systemic reaction - Disutility associated with anaphylaxis - Disutility associated with Guillain-Barre syndrome - Disutility associated with long-term sequelae (<18 years) - Disutility due to premature death - Life expectancy in years
Economic results	**Type of summary ratio**	Primary outcome was the incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted life years (QALYs) gained	
	Overall payer perspective result	**Scenario analysis** ▪ NHR - 6-23 months ICER vaccination versus no vaccination $20,000/QALY gained - 2-4 years ICER vaccination versus no vaccination $13,000/QALY gained - 5-11 years ICER vaccination versus no vaccination $27,000/QALY gained	

		- 12-17 years ICER vaccination versus no vaccination $41,000/QALY gained - 18-49 years ICER vaccination versus no vaccination $131,000/QALY gained - 50-64 years ICER vaccination versus no vaccination $50,000/QALY gained ▪ HR - 6-23 months ICER vaccination versus no vaccination – Cost saving - 2-4 years ICER vaccination versus no vaccination – Cost saving - 5-11 years ICER vaccination versus no vaccination $5,000/QALY gained - 12-17 years ICER vaccination versus no vaccination $8,000/QALY gained - 18-49 years ICER vaccination versus no vaccination $4,000/QALY gained - 50-64 years ICER vaccination versus no vaccination – Cost saving - ≥65 years ICER vaccination versus no vaccination – Cost saving
	Overall societal perspective result	▪ NHR - 6-23 months ICER vaccination versus no vaccination $45,000/QALY gained - 2-4 years ICER vaccination versus no vaccination $32,000/QALY gained - 5-11 years ICER vaccination versus no vaccination $63,000/QALY gained - 12-17 years ICER vaccination versus no vaccination $95,000/QALY gained - 18-49 years ICER vaccination versus no vaccination $194,000/QALY gained - 50-64 years ICER vaccination versus no vaccination $80,000/QALY gained ▪ HR - 6-23 months ICER vaccination versus no vaccination $12,000/QALY gained - 2-4 years ICER vaccination versus no vaccination $1,500/QALY gained - 5-11 years ICER vaccination versus no vaccination $29,000/QALY gained - 12-17 years ICER vaccination versus no vaccination $40,000/QALY gained - 18-49 years ICER vaccination versus no vaccination $23,000/QALY gained - 50-64 years ICER vaccination versus no vaccination – Cost saving - ≥65 years ICER vaccination versus no vaccination – Cost saving Alternate strategies only presented as threshold analyses of vaccine effectiveness for RIV4, aIIV4, HD-IIV4 compared to vaccination programme strategy and compared to no vaccination.
Authors conclusions	Results indicate that influenza vaccination produces cost-effectiveness ratios that are less than commonly used cost-effectiveness thresholds for most subgroups. Vaccination for non-high-risk working-age adults exceeds commonly used cost-effectiveness thresholds of $100,000/QALY and $150,000/QALY, but results are especially sensitive to changes in the probability of influenza illness. After incorporating updated epidemiologic and vaccine effectiveness data, routine annual influenza vaccination remains attractive for most age and risk groups from an economic perspective.	

Key: aIIV4 – adjuvanted quadrivalent inactivated influenza vaccine; AR – all risk; CUA – cost-utility analysis; HD-IIV4 – high-dose quadrivalent inactivated influenza vaccine; HR – high risk; NHR – non-high-risk; ICER – incremental cost effectiveness ratio; OTC – over-the-counter; PSA – Probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; RIV4 – recombinant quadrivalent influenza vaccine; US – United States; USD – United States dollars.

General study characteristics	**Author name** **Year of publication** **DOI**	Kohli 2021 10.1080/21645515.2021.1971017	
	Region or country	UK	
	Type of economic evaluation	CUA	
	Population	Entire population (Note: Model includes all JCVI-recommended and NHS-funded vaccines for 2021/2022 season. Data extraction only includes vaccination of target group aged ≥65yrs.)	
	Funding	Seqirus	
Model characteristics	**Model type**	Dynamic transmission model (epidemiology) and decision tree (economic)	
	Perspective	NHS and Personal Social Services (public sector)	
	Time horizon	10 influenza seasons (results presented as average annual values)	
	Comparator	HD-QIV (when intervention aQIV) aQIV (when intervention HD-QIV)	
	Discount rates	3.5% for both costs and outcomes	
	Sensitivity analysis	Vaccine pricing analysis for HD-QIV and various scenario analyses	
Intervention strategy	**Dosing schedule**	1-dose	
	Vaccine type (intervention)	aQIV and HD-QIV	
	Age at vaccination	≥65 years	
	Coverage rate	65-74yrs: 68.0% ≥75yrs: 80%	
Model input parameters	**Efficacy/effectiveness**	Three rVE scenarios rVE of aQIV versus HD-QIV in preventing influenza: -2.5%, 3.2% and 8.9% (based on study demonstrating relative VE of aTIV v HD-TIV, corresponding to the point estimate and bounds of the confidence interval)	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ Outpatient medical costs to include: - consultations for influenza - broad-spectrum antibiotics associated with complications for influenza such as otitis media, pneumonia, and sinusitis - anti-viral treatment for high-risk individuals ▪ Hospitalisation ▪ Vaccination costs - vaccine - vaccine administration **Indirect costs** ▪ Not applicable	**Measurement and valuation** **Direct costs** ▪ Medical costs - cost of outpatient care (by risk and age group) - cost of hospital admission (by risk and age group) ▪ Vaccination costs - ex-vat unit price of vaccine - vaccine administration cost assumed the same regardless of type of vaccine used **Indirect costs** ▪ Not applicable
	Effects included	**Type of effects** **Direct effects** ▪ Uncomplicated influenza ▪ Hospitalisation for influenza ▪ Death due to premature influenza-related death **Indirect effects** ▪ Reduced virus transmission in entire population	**Measurement and valuation** **Direct effects** ▪ Proportion at high risk of complication if infected (by age group) ▪ Probability of hospitalisation given infection (by risk and age group) ▪ Case fatality rate (per 1,000 hospitalised cases) (by risk and age group) **Indirect effects** ▪ Clinical influenza cases in population ▪ Hospitalisations in entire population

			▪ Deaths in entire population **QALYs** ▪ Average disutility for uncomplicated case of influenza ▪ Average disutility for hospitalised case of influenza ▪ QALYs lost due to death not provided (calculated from expected survival and expected age-specific utility values).
Economic results	**Type of summary ratio**	ICER (per QALY gained)	
	Overall NHS and personal social services perspective result	aQIV v HD-QIV: aQIV is cost saving compared with HD-QIV. HD-QIV v aQIV: In order for the ICER of HD-QIV, compared with aQIV, to fall below a cost per QALY WTP threshold of £20,000, the unit price of HD-QIV needs to be less than £12.94 if the relative VE of aQIV (compared to HD-QIV) is −2.5%, less than £10.44 if the relative VE is 3.2% and less than £7.67 if the relative VE is 8.9%.	
	Overall societal perspective result	Not applicable	
Authors conclusions	Given the effectiveness evidence, aQIV is cost saving compared to HD-QIV, assuming HDQIV is priced at the existing list price of HD-TIV.		

Key: aQIV – adjuvanted quadrivalent influenza vaccine; CUA – cost-utility analysis; HD-QIV – high-dose quadrivalent influenza vaccine; HD-TIV – high-dose trivalent influenza vaccine; JCVI – joint committee on immunisation and vaccination; ICER – incremental cost effectiveness ratio; NHS – national health service; QALY – quality-adjusted life year; rVE – relative vaccine effectiveness; UK – United Kingdom; VE – vaccine effectiveness; WTP – willingness-to-pay.

General study characteristics	**Author name** **Year of publication** **DOI**	Kohli 2022 10.3390/vaccines10091386
	Region or country	Germany
	Type of economic evaluation	CUA
	Population	German population ≥65 years (entire population modelled but results presented for target group)
	Funding	Seqirus US
Model characteristics	**Model type**	Compartmental transmission model calibrated to outpatient visits for influenza in Germany (SEIR) Reported time step of 0.1 days Health states: susceptible non-vaccinated, susceptible vaccinated, exposed non-vaccinated, exposed vaccinated, infected non-vaccinated, infected vaccinated, recovered non-vaccinated, recovered vaccinated Resource use decision-tree model for medically attended infections – inpatient complications (acute otitis media, pneumonia, severe influenza), no complications, outpatient complications (acute otitis media, pneumonia) which culminate in influenza-related death or no influenza-related death
	Perspective	Base case analyses used the societal perspective Sensitivity analyses used the Statutory Health Insurance payer perspective
	Time horizon	10 influenza seasons
	Comparator	aQIV vs standard QIV (comparator) and aQIV vs HD-QIV (comparator)
	Discount rates	3% for both costs and QALYs
	Sensitivity analysis	Deterministic sensitivity analysis, probabilistic sensitivity analysis, scenario analyses – altered number of severe flu seasons, alternate vaccine efficacies from publications, threshold analyses.
Intervention strategy	**Dosing schedule**	Not applicable
	Vaccine type (intervention)	aQIV
	Age at vaccination	≥65 years (entire population modelled but results presented for target group ≥65 years)
	Coverage rate	▪ Low risk 6-23 months: 4.7% 2-6 years: 4.7% 7-17 years: 4.6% 18-49 years: 17.2% 50-59 years: 23.4% 60-64 years: 40% ≥65 years: 40% ≥75 years: 40% ▪ High risk 6-23 months: 9.3% 2-6 years: 9.3% 7-17 years: 9.2% 18-49 years: 34.4% 50-59 years: 46.8% 60-64 years: 40% ≥65 years: 40% ≥75 years: 40%
Model input parameters	**Efficacy/effectiveness**	▪ Standard QIV 62% against A/H1N1 24% against A/H3N2 79% against B types rVE of aTIV compared to standard TIV for reducing medical encounters: 13.9% rVE of aTIV compared to HD-TIV for reducing medical encounters: 3.2% (not statistically significant)

		Assume rVE of quadrivalent versions same as trivalent versions based on non-inferior immune response in RCT	
	Waning	Not applicable	
	Costs included	**<u>Type of cost</u>** **Direct costs** ▪ Cost of vaccine ▪ Cost of administration ▪ Cost of hospital admission ▪ Cost of medical care visits **Indirect costs** ▪ Sickness benefit ▪ Productivity costs	**<u>Measurement and valuation</u>** **Direct costs** ▪ Cost of hospital admission (age group stratified) ▪ Cost of outpatient medical care visits (age group stratified) **Vaccine related costs** ▪ Cost of standard QIV ▪ Cost of aQIV ▪ Cost of QIV-HD ▪ Cost of vaccine administration **Indirect costs** ▪ Sickness benefit (age group stratified) – received for parental absenteeism for sick child ▪ Cost of time lost from work was estimated using a human capital approach (applies to 18-64 years). Daily wage loss and number of days, included.
	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Medically attended influenza cases ▪ Outpatient complications ▪ Hospitalisations ▪ Death	**<u>Measurement and valuation</u>** **Direct effects** ▪ Proportion of population at high risk of complication if infected (age group stratified) ▪ Probability of hospitalisation for medically attended cases (age group stratified) ▪ Case fatality risk (age group stratified, HR, NHR) **QALY loss** ▪ Baseline utility values: (age group stratified, HR, NHR) - QALY loss Uncomplicated influenza (age group stratified, HR, NHR) - QALY loss of outpatient AOM - QALY loss of hospitalised AOM - QALY loss of outpatient CAP - QALY loss of inpatient CAP - QALY loss of all other hospitalisations for influenza - QALY loss due to premature death
Economic results	**Type of summary ratio**	Incremental cost per QALY	
	Overall payer perspective result	▪ aQIV vs standard QIV - Base case (4 severe seasons) ICER €17,200 per QALY gained - Scenario (2 severe seasons) ICER €20,000 per QALY gained - Scenario (0 severe seasons) ICER €26,000 per QALY gained ▪ aQIV vs QIV-HD - Base case (4 severe seasons) aQIV dominated QIV-HD - Scenario (2 severe seasons) aQIV dominated QIV-HD - Scenario (0 severe seasons) aQIV dominated QIV-HD	
	Overall societal perspective result	▪ aQIV vs standard QIV - Base case (4 severe seasons) ICER €14,500 per QALY gained - Scenario (2 severe seasons) ICER €17,200 per QALY gained	

		- Scenario (0 severe seasons) ICER €23,000 per QALY gained ▪ aQIV vs QIV-HD - Base case (4 severe seasons) aQIV dominated QIV-HD - Scenario (2 severe seasons) aQIV dominated QIV-HD - Scenario (0 severe seasons) aQIV dominated QIV-HD
Authors conclusions	This analysis demonstrated that aQIV may be cost effective compared to the standard QIV depending on the WTP for additional benefits given current clinical evidence. As aQIV and HD-QIV are similar in terms of effectiveness, aQIV is cost saving compared to HD-QIV at current unit prices.	

Key: AOM- acute otitis media; aQIV – adjuvanted quadrivalent influenza vaccine; aTIV – adjuvanted trivalent influenza vaccine; CAP – community acquired pneumonia; CUA – cost-utility analysis; HD-QIV – high-dose quadrivalent influenza vaccine; HD-TIV – high-dose trivalent influenza vaccine; HR – high risk; ICER – incremental cost-effectiveness ratio; NHR – non-high-risk; QALY – quality-adjusted life year; RCT – randomised controlled trial; Standard QIV – standard quadrivalent influenza vaccine; Standard TIV – standard trivalent influenza vaccine; SEIR model – susceptible, exposed, infected, recovered model; SHI – statutory health insurance; rVE – relative vaccine effectiveness; USA – United States of America; WTP – willingness-to-pay.

General study characteristics	**Author name** **Year of publication** **DOI**	Marbaix 2023 10.1080/14760584.2023.2229917	
	Region or country	Belgium	
	Type of economic evaluation	CEA and CUA	
	Population	≥65 years (divided into age subgroups: 65-74 years and ≥75 years)	
	Funding	Seqirus CSL	
Model characteristics	**Model type**	Static decision-tree model	
	Perspective	National healthcare payer perspective	
	Time horizon	Influenza season, namely within one year. Model accounted for potential years of life lost beyond the influenza season.	
	Comparator	Standard QIV (base case), HD-QIV (scenario)	
	Discount rates	Life years lost were estimated based on life expectancy data for those aged ≥65 annually discounted at 1.5%	
	Sensitivity analysis	Deterministic one-way sensitivity analysis, PSA, Scenario analysis considered 0% and 5% discount rates	
Intervention strategy	**Dosing schedule**	One dose	
	Vaccine type (intervention)	aQIV	
	Age at vaccination	≥65 years	
	Coverage rate	65-74 years: 53.2% ≥75 years: 70.8%	
Model input parameters	**Efficacy/effectiveness**	aQIV: 56.1% (calculated using rVE of aTIV compared to HD-TIV) HD-QIV: 54.7% (calculated using rVE of HD-TIV compared to standard TIV) Standard QIV: 40.2% Assumed rVE of QIV vaccines is the same as TIVs	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ Ambulatory cost of influenza symptoms ▪ Influenza with complications managed in ambulatory care ▪ Influenza with complications managed in hospital ▪ Patient costs-co-payments **Vaccine related costs** ▪ Vaccine acquisition cost ▪ Vaccine administration cost **Indirect costs** Not applicable	**Measurement and valuation** **Direct costs** ▪ Cost of ambulatory care of influenza infection ▪ Cost of hospitalisation due to influenza complications - Bronchitis/URTI - Pneumonia - Myocarditis/Myocardial infarction - Renal complications - CNS complications - COPD exacerbations - Stroke ▪ Cost of complications in ambulatory care - Bronchitis/URTI - Pneumonia/COPD exacerbations ▪ Patient costs – co-payments for all of the above costs ▪ Duration of hospitalisation **Vaccine related costs** ▪ Cost of aQIV ▪ Cost of standard QIV ▪ Cost of HD-QIV ▪ Vaccine administration cost: GP visit **Indirect costs** Not applicable

	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Medically attended cases of influenza ▪ Hospitalisation ▪ Influenza related mortality ▪ Life years **Indirect effects** Not applicable	**<u>Measurement and valuation</u>** **Direct effects** ▪ Influenza attack rate among unvaccinated adults aged ≥65 years ▪ Probability of influenza infection after each vaccination alternative ▪ Influenza incidence rate among standard QIV vaccinated patients ▪ Proportion of patients seeking ambulatory professional care (age group stratified) ▪ Probability of developing following influenza related complications, % hospitalisation rate of complications, % mortality rate of complications (conditional on hospitalisation) - Bronchitis (age group stratified) - Pneumonia (age group stratified) - URTI (age group stratified) - Myocarditis (age group stratified) - Renal complications (age group stratified) - CNS complications (age group stratified) - COPD exacerbations (age group stratified) - Myocardial infarction (age group stratified) - Stroke (age group stratified) **QALY loss per case** ▪ Baseline healthy utility: 65-74 years and ≥75 years - Disutility and duration of symptomatic influenza - Disutility of influenza related URTI in ambulatory setting - Disutility of influenza related bronchitis in ambulatory setting - Disutility of influenza related pneumonia in ambulatory setting - Disutility of influenza related COPD in ambulatory setting - Disutility of hospitalisations due to MI or stroke - Disutility and duration of hospitalisation due to complications other than MI or stroke
Economic results	**Type of summary ratio**	Incremental cost per LY gained and incremental cost per QALY gained	
	Overall payer perspective result	ICER aQIV vs standard QIV = €15,227/QALY gained The probability of aQIV being cost-effective was estimated to be 82% at a WTP threshold of €35,000. ICER aQIV vs standard QIV = €15,967/LY gained	
	Overall societal perspective result	Not applicable	
Authors conclusions	Analysis suggested that aQIV is cost effective compared to standard QIV, with an ICER of €15,227/QALY from a public payer perspective. Increasing the attack rate from 5% to 7.2% decreased the ICER to €7,608/QALY. When compared to HD-QIV, aQIV is cost saving, with an at least similar effectiveness.		

Key: aQIV – adjuvanted quadrivalent influenza vaccination; aTIV – adjuvanted trivalent influenza vaccine; CEA – cost-effectiveness analysis; CNS – central nervous system; COPD – chronic obstructive pulmonary disease; CUA – cost-utility analysis; GP – general practitioner; HD-QIV – high-dose quadrivalent influenza vaccine; HD-TIV – high-dose trivalent influenza vaccine; ICER – incremental cost-effectiveness ratio; LY – life year; MI – myocardial infarction; PSA – Probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; rVE – relative vaccine effectiveness; QIV – quadrivalent influenza vaccine; TIV – trivalent influenza vaccine; URTI – upper respiratory tract infection; WTP – willingness-to-pay.

General study characteristics	**Author name** **Year of publication** **DOI**	Mattock 2021 10.1080/13696998.2021.2000780	
	Region or country	England and Wales	
	Type of economic evaluation	CUA	
	Population	Adults ages ≥65 years in England and Wales Stratified into 3 groups according to age and risk of influenza related complications 1. 65-74 years at high risk (chronic respiratory disease or chronic heart disease) of complications 2. 65-74 years at low risk of complications, without underlying medical conditions 3. All people aged ≥75 years including both low- and high-risk groups	
	Funding	Sanofi Pasteur	
Model characteristics	**Model type**	Decision tree Two disease pathways following vaccination 1. Laboratory-confirmed influenza cases that could result in GP visit 2. Hospital stays which could lead to premature death	
	Perspective	Healthcare perspective (costs to NHS and prescribed specialised services)	
	Time horizon	A single influenza season QALYs over a lifetime horizon	
	Comparator	aTIV	
	Discount rates	No discounting on costs as these occurred within a year of vaccination 3.5% on QALYs occurring after 12 months	
	Sensitivity analysis	One-way deterministic sensitivity analysis (95% CI or +/- 15%) rVE scenarios for aTIV and HD-TIV, threshold analysis on cost of HD-TIV Secondary analysis using expanded hospitalisation definition (altered hospitalisation rates, VE and costs)	
Intervention strategy	**Dosing schedule**	Not specified (but both vaccines are 1-dose)	
	Vaccine type (intervention)	HD-TIV	
	Age at vaccination	See population	
	Coverage rate	65-74 years (all risk): 62.7% ≥75 years (all risk): 80.0%	
Model input parameters	**Efficacy/effectiveness**	▪ Base case (scenario 1) - rVE of HD-TIV vs standard TIV against laboratory-confirmed influenza: 24.2% - rVE of HD-TIV vs standard TIV against hospitalisation: 24.3% - rVE of aTIV vs standard TIV against laboratory-confirmed influenza: 0% - rVE of aTIV vs standard TIV against hospitalisation: 0% - VE of standard TIV vs no vaccination against matched laboratory-confirmed influenza: 46.0% - VE of standard TIV vs no vaccination against mismatched laboratory-confirmed influenza: 28.0% - VE of standard TIV vs no vaccination against hospitalisation: 28.0% ▪ Scenario 2 and 3 – difference in aTIV only - rVE of aTIV vs standard TIV against laboratory-confirmed influenza 10.0% and 20.0% - rVE of aTIV vs standard TIV against hospitalisation 6.0% and 12.0%	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ GP visits ▪ Hospitalisation **Vaccine related costs** ▪ Vaccine acquisition costs	**Measurement and valuation** **Direct costs** ▪ Cost per GP consultation (£) – which included the mean primary care staff and prescription costs per influenza episode ▪ Cost of hospitalisation (£) **Vaccine related costs** ▪ Cost of aTIV (£)

			▪ Cost of HD-TIV (£)
	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Influenza cases ▪ GP visit ▪ Hospitalisation ▪ Influenza-related mortality in hospitalised patients	**<u>Measurement and valuation</u>** **Direct effects** ▪ Influenza attack rate (unvaccinated) ▪ Total number of influenza in population ▪ Probability of lab-confirmed influenza ▪ Probability of lab-confirmed influenza in vaccinated ▪ Probability of GP visit- age group stratified ▪ Number of GP attendances due to influenza ▪ Probability of hospitalisation adjusted for vaccination/non-vaccination ▪ Hospitalisation rate per 100,000 vaccinated with standard TIV- age and risk stratified as per defined groups ▪ Probability of mortality following hospitalisation by age group ▪ Age standardised mortality rates **QALY loss per case** ▪ Life expectancy – gender weighted and by age group ▪ Baseline utility values – by age group stratified (based on EQ5D) ▪ Utility of LCI case ▪ Duration of LCI influenza infection ▪ Disutility of influenza related hospitalisation ▪ QALY loss due to premature mortality
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	▪ Base case ICER aggregated in ≥65 years (all risk) HD-TIV vs aTIV = £1,932/QALY ▪ Base case ICER in 65-74 years (all risk) HD-TIV vs aTIV = £14,175/QALY ▪ Base case ICER in ≥75 years (all risk) HD-TIV vs aTIV = Dominant ▪ Scenario 2 ICER aggregated in ≥65 years (all risk) HD-TIV vs aTIV = £4,181/QALY ▪ Scenario 2 ICER in 65-74 years (all risk) HD-TIV vs aTIV = £21,165/QALY ▪ Scenario 2 ICER in ≥75 years (all risk) HD-TIV vs aTIV = £781/QALY ▪ Scenario 3 ICER aggregated in ≥65 years (all risk) HD-TIV vs aTIV = £8,767/QALY ▪ Scenario 3 ICER in 65-74 years (all risk) HD-TIV vs aTIV = £36,460/QALY ▪ Scenario 3 ICER in ≥75 years (all risk) HD-TIV vs aTIV = £3,533/QALY Secondary analysis (respiratory hospitalisations) £2,800/QALY	
	Overall societal perspective result	Not applicable	
Authors conclusions	HD-TIV as cost-effective versus aTIV in populations aged ≥65 years, when adopting a healthcare payer perspective and assuming a CE threshold of £20,000 per QALY. The results of the uncertainty analysis showed the cost effectiveness of HD-TIV was robust to changes in the majority of parameter values. Vaccination with HD-TIV instead of aTIV substantially reduced influenza related GP visits, hospitalizations, and mortality.		

Key: aTIV – adjuvanted trivalent influenza vaccine; CE – cost-effectiveness; CI – confidence interval; CUA – cost-utility analysis; GP – general practitioner; HD-TIV – high-dose trivalent influenza vaccine; ICER – incremental cost-effectiveness ratio; LCI – laboratory confirmed influenza; NHS – national health service; QALY – quality-adjusted life yearquality-adjusted life year; rVE – relative vaccine effectiveness; standard TIV – standard-dose trivalent influenza vaccine; VE – vaccine effectiveness.

General study characteristics	**Author name** **Year of publication** **DOI**	Nguyen 2022 10.3390/vaccines10081257
	Region or country	Canada
	Type of economic evaluation	CUA
	Population	Canadian population aged ≥65 years
	Funding	Seqirus Canada (a subsidiary of Novartis developing ccQIV)
Model characteristics	**Model type**	Age-structured four-strain dynamic SEIR transmission model. Health states include: GP visit; ER visit, Hospitalisation requiring ICU admission; Hospitalisation not requiring ICU admission Unspecified cycle length
	Perspective	Not specified – assume healthcare payer as costed based on healthcare resource utilisation
	Time horizon	8 years (2012-2019)
	Comparator	Standard QIV
	Discount rates	5%
	Sensitivity analysis	PSA
Intervention strategy	**Dosing schedule**	Standard QIV (6 months to 64 years) + aTIV (for ≥65 years) Standard QIV (6 months to 64 years) + HD-QIV (HD-QIV for ≥65 years) ccQIV (6 months to 64 years) + aTIV (≥65 years)
	Vaccine type (intervention)	ccQIV or standard QIV aTIV HD-QIV
	Age at vaccination	Not specified – see dosing schedule.
	Coverage rate	6 months to 54 years (general population and high risk): 29% 55 to 64 years (general population and high risk): 47% ≥65 years (general population and high risk): 75%
Model input parameters	**Efficacy/effectiveness**	**Absolute VE (standard QIV)** ▪ A/H1N1 - 2012: 59% - 2013: 71% - 2014: 9% - 2015: 43% - 2016: 36% - 2017: 58% - 2018: 67% - 2019: 43% ▪ A/H3N2 - 2012: 41% - 2013: 66% - 2014: 9% - 2015: 44% - 2016: 36% - 2017: 14% - 2018: 17% - 2019: 50% ▪ BVIC - 2012: 68% - 2013: 72% - 2014: 9%

		- 2015: 50% - 2016: 72% - 2017: 46% - 2018: 72% - 2019: 65% BYAM - 2012: 68% - 2013: 72% - 2014: 9% - 2015: 50% - 2016: 72% - 2017: 46% - 2018: 72% - 2019: 65% **rVE (ccQIV when egg-adapted):** 15.6% rVE HD-QIV vs aTIV when egg adapted: 9% rVE HD-QIV vs aTIV when matched: 24%	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ GP visit costs ▪ ED costs ▪ Hospitalisation costs ▪ ICU cost ▪ ICU and mechanical ventilation costs ▪ ICU and ECMO cost **Vaccine costs** ▪ Vaccine price	**Measurement and valuation** **Direct costs** ▪ GP visit costs in CAD ▪ ED costs in CAD ▪ Hospitalisation costs in CAD ▪ ICU cost in CAD ▪ ICU and mechanical ventilation costs in CAD ▪ ICU and ECMO cost in CAD ▪ Probability of GP cases – all age groups ▪ Probability of Hospitalisation – by age groups (conditional on symptomatic case) ▪ Probability of ICU admission – by age group (conditional on hospitalisation) ▪ Probability of Mechanical ventilation requirement – by age group (conditional on ICU admission) ▪ Probability of ECMO requirement by age group (conditional on ICU admission) ▪ Probability of Mortality – by age group (conditional on hospitalisation) **Vaccine related** ▪ Vaccine price in CAD (reported in text but not provided)
	Effects included	**Type of effects** **Direct effects** ▪ Incidence of influenza ▪ Symptomatic cases ▪ GP consultations ▪ ED consultations ▪ Hospitalisation ▪ ICU hospitalisations ▪ Death	**Measurement and valuation** **Direct effects** ▪ Incidence of influenza taken from epidemiological model ▪ Probability of GP cases – all age groups ▪ Probability of Hospitalisation – by age groups (conditional on symptomatic case) ▪ Probability of ICU admission – by age group (conditional on hospitalisation)

			▪ Probability of Mechanical ventilation requirement – by age group (conditional on ICU admission) ▪ Probability of ECMO requirement by age group (conditional on ICU admission) ▪ Probability of Mortality – by age group (conditional on hospitalisation) **QALY loss per case** ▪ QALY loss from symptomatic cases – age group stratified ▪ QALY loss from death – age group stratified
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	Base case Standard QIV (6 months to 64 years) + aTIV (≥65 years) vs standard QIV for all (ref case)=Cost saving Standard QIV (6 months to 64 years) + HD-QIV (≥65 years) vs ref case= 81,300/QALY ccQIV (6 months to 64 years) + aTIV (≥65 years) vs ref case= 1,300/QALY	
	Overall societal perspective result	Not applicable	
Authors conclusions	Vaccination of those aged 6 months to 64 years with a ccQIV together with aTIV for those aged ≥65 years is cost effective across varying assumptions of rVE and numbers of egg-adapted influenza seasons. Overall, this vaccine combination resulted in the greatest reductions in cases, hospitalisations, and deaths due to influenza compared with the other scenarios evaluated. While the incremental advantages of ccQIV and aTIV will vary between individual influenza seasons, sensitivity analysis reveals that this vaccine combination would be favourable in nearly all scenarios. The higher cost of an individual dose of a HD-QIV vaccine underpinned the cost-effectiveness analysis, with none of the standard QIV and HD-QIV scenarios being cost effective, despite improvements in terms of case numbers, hospitalisations, and deaths compared with the baseline scenario.		

Key: aTIV – adjuvanted trivalent influenza vaccine; CAD – Canadian dollars; ccQIV – cell-based quadrivalent influenza vaccine; CUA – Cost-utility analysis; ECMO – extracorporeal membrane oxygenation; ED – emergency department; ER – emergency room; GP – general practitioner; HD-QIV – high-dose quadrivalent influenza vaccine; ICER – incremental cost effectiveness ratio; ICU – intensive care unit; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccine; rVE – relative vaccine effectiveness; Standard QIV – standard quadrivalent influenza vaccine; SEIR – susceptible, exposed, infectious, recovered; VE – vaccine effectiveness.

General study characteristics	**Author name** **Year of publication** **DOI**	Nguyen 2023 10.3390/vaccines11050933
	Region or country	Ireland
	Type of economic evaluation	CUA
	Population	≥65 years
	Funding	Seqirus Inc
Model characteristics	**Model type**	Age structured, four strain (strains A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) dynamic SEIR model, Decision tree of outcomes from symptomatic infected in high or low risk – non-medically attended, GP visit, hospitalisation, death conditional on hospitalisation
	Perspective	Payer (healthcare) Societal
	Time horizon	Not specified
	Comparator	QIV
	Discount rates	LYs and QALYs discounted at 3%
	Sensitivity analysis	Included but not specified which form Sensitivity analysis for influenza incidence, relative vaccine effectiveness, excess mortality and impact of co-circulating influenza and COVID-19
Intervention strategy	**Dosing schedule**	QLAIV children 2-17 QIV at risk patients 18-64 years Adults ≥65 years QIV or aQIV
	Vaccine type (intervention)	aQIV
	Age at vaccination	Not specified – see dosing schedule
	Coverage rate	**Current scenario** ▪ Low risk - 6-23 months: 0% - 2-17 years: 27.6% - 18-49 years: N/A - 50-64 years: N/A - 65-74 years: 68.0% - ≥75 years: 80.0% ▪ High risk - 6-23 months: 3.10% - 2-17 years 48.6% - 18-49 years: 48.6% - 50-64 years: 48.6% - 65-74 years: 68.0% - ≥75 years: 80.0% **aQIV Scenario** ▪ Low risk - 6-23 months: 0% - 2-17 years: 27.6% - 18-49 years: N/A - 50-64 years: 40.0% - 65-74 years: 68.0% - ≥75 years: 80.0% ▪ High risk - 6-23 months: 3.1%

		- 2-17 years: 48.6% - 18-49 years: 48.6% - 50-64 years: 48.6% - 65-74 years: 68.0% - ≥75 years: 80.0%	
Model input parameters	**Efficacy/effectiveness**	**VE QIV** - 6-23 months: 62.5% - 2-17 years: 62.5% - 18-49 years: 54.0% - 50-64 years: 54.0% - 65-74 years: 47.8%% - ≥75 years: 45.3% **VE aQIV** - 6-23 months: N/A - 2-17 years: N/A - 18-49 years: N/A - 50-64 years: N/A - 65-74 years: 55.0% - ≥75 years: 52.9% **VE QLAIV** - 6-23 months: N/A - 2-17 years: 62.5% - 18-49 years: N/A - 50-64 years: N/A - 65-74 years: N/A - ≥75 years: N/A **rVE for aQIV vs QIV for base case scenario:**13.9%	
	Waning	Assumed infection or vaccine induced protection did not wane during season	
	Costs included	**<u>Type of cost</u>** **Direct costs** ▪ GP costs ▪ Hospitalisation costs **Vaccine related costs** ▪ Vaccine acquisition prices ▪ Vaccine administration **Indirect costs** ▪ Productivity loss due to GP visit – low-risk patient ▪ Productivity loss due to GP visit – high-risk patient ▪ Productivity loss due to hospitalisation – low-risk patient ▪ Productivity loss due to hospitalisation – high-risk patient	**<u>Measurement and valuation</u>** **Direct costs** ▪ Probability of GP visits for low-risk case – age group stratified ▪ Probability of GP visit for high-risk case – age group stratified ▪ Probability of hospitalisation for low-risk case – age group stratified ▪ Probability of hospitalisation for high-risk case – age group stratified ▪ Probability of death conditional on hospitalisation for low-risk case – age group stratified ▪ Probability of death conditional on hospitalisation for high-risk case – age group stratified **Vaccine costs** ▪ Price of QIV (€) ▪ Price of aQIV (€) ▪ Price of QLAIV (€) **Indirect costs** ▪ Productivity loss due to GP visit – low-risk patient in days

			▪ Productivity loss due to GP visit – high-risk patient in days ▪ Productivity loss due to hospitalisation – low-risk patient in days ▪ Productivity loss due to hospitalisation – high-risk patient in days ▪ Average wages in Ireland per year
	Effects included	**Type of effects** **Direct effects** ▪ Symptomatic non-medically attended cases ▪ Symptomatic GP visits ▪ Symptomatic hospitalisations ▪ Mortality conditional on influenza hospitalisation ▪ Life years lost	**Measurement and valuation** **Direct effects** ▪ Proportion of population starting season (pre-vaccination) protected from influenza (clinical or subclinical) ▪ Probability of influenza transmission ▪ Influenza virus attack rate – age group stratified by contact matrix estimates ▪ Probability of GP visits for low-risk case – age group stratified ▪ Probability of GP visit for high-risk case – age group stratified ▪ Probability of hospitalisation for low-risk case – age group stratified ▪ Probability of hospitalisation for high-risk case – age group stratified ▪ Probability of death conditional on hospitalisation for low-risk case – age group stratified ▪ Probability of death conditional on hospitalisation for high-risk case – age group stratified **QALY loss per case** ▪ QALY associated with outpatient visit ▪ QALY associated with inpatient visit ▪ QALY loss from premature death
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	aQIV in individuals ≥65 years compared to current vaccination scenario: ICER €12,970	
	Overall societal perspective result	aQIV in ≥65 years compared to current vaccination scenario: ICER €2,420	
Authors conclusions	The use of aQIV in adults ≥65 years in Ireland was shown to be cost effective, with an ICER of €2,420–€12,970. This ICER estimate was robust to sensitivity analysis for the influenza influence and strain prevalence, with all scenarios evaluated with an rVE >3% for aQIV vs QIV, resulting in ICERs considerably below the €45,000 threshold. The use of aQIV in older adults was also shown to result in a modest reduction in excess bed occupancy against a background of co-circulating COVID-19 and influenza.		

Key: aQIV – adjuvanted quadrivalent influenza vaccine; CUA – cost-utility analysis; GP – general practitioner; ICER – incremental cost effectiveness ratio; LYs – life years; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccine; QLAIV – quadrivalent live-attenuated influenza vaccine; rVE – relative vaccine effectiveness; SEIR – susceptible, exposed, infected, recovered; VE – vaccine effectiveness.

General study characteristics	**Author name** **Year of publication** **DOI**	Redondo 2021 10.1016/j.vaccine.2021.07.048	
	Region or country	Spain	
	Type of economic evaluation	CUA	
	Population	≥65 years	
	Funding	Sanofi Pasteur	
Model characteristics	**Model type**	Decision-tree model	
	Perspective	Healthcare system	
	Time horizon	6 months – all outcomes LYs and QALYs over lifetime horizon also presented	
	Comparator	aTIV	
	Discount rates	Not applicable to costs and health outcomes within 6 months, LYs and QALYs lost due to premature death discounted by 3%	
	Sensitivity analysis	Deterministic – one-way, and probabilistic sensitivity analyses. Scenario analyses – including broader definition of hospitalisation causes and alternate rVE	
Intervention strategy	**Dosing schedule**	Not specified	
	Vaccine type (intervention)	HD-QIV	
	Age at vaccination	Not specified	
	Coverage rate	65-74 years: 46.9% ≥75 years: 57.8%	
Model input parameters	**Efficacy/effectiveness**	▪ Standard TIV VE against strains A and B match in those aged ≥65 years: 50% ▪ Standard TIV VE against strain B mismatch in those aged ≥65 years: 35% ▪ Relative VE HD-QIV vs standard TIV against flu case: 24.2% ▪ Relative VE HD-QIV vs standard TIV against flu hospitalisation: 24.3% ▪ Relative VE aTIV vs standard TIV against flu cases and against flu hospitalisation: 6%	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ GP costs ▪ ED visit costs ▪ Hospitalisation costs **Vaccine related costs** ▪ Vaccine acquisition price ▪ Vaccine administration cost	**Measurement and valuation** **Direct costs** ▪ GP visit unit cost (€) ▪ ED visit unit cost (€) ▪ Cost of influenza and pneumonia hospitalisation (€)– age group stratified ▪ Cost of hospitalisation for respiratory and cardiovascular cause (€)– age group stratified **Vaccine related costs** ▪ HD-QIV list price (€) ▪ aTIV list price (€) ▪ Vaccine administration cost (€)
	Effects included	**Type of effects** **Direct effects** ▪ Number of influenza cases (population level) ▪ Number of GP visits related to influenza ▪ Number of ED presentations related to influenza ▪ Number of hospitalisations related to influenza ▪ Number of deaths occurring during influenza season ▪ Life years lost to premature mortality	**Measurement and valuation** **Direct effects** ▪ Influenza attack rate without vaccine ▪ Proportion circulating type A flu ▪ Proportion circulating type B flu matched with vaccine ▪ Excess mortality attributable to influenza – rate per 100000 ▪ Probability of visit to GP for influenza ▪ Probability of emergency department visit for influenza ▪ Hospitalisation rate per 100,000 people influenza and pneumonia

			▪ Hospitalisation rate per 100,000 people respiratory and cardiovascular causes ▪ Percentage hospitalisations attributable to pneumonia, cardiovascular and respiratory causes during flu season **QALY loss per case** ▪ Base utility – age group stratified ▪ Loss of utility due to influenza ▪ Loss of utility due to hospitalisation ▪ Duration of influenza episode in days ▪ Length of stay in days
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	▪ HD-QIV vs aTIV – ICER €24,353/QALY ▪ Scenario – adjuvanted rVE 0% against hospitalisation and broader definition of hospitalisation causes – HQ-QIV dominated aTIV ▪ Probabilistic sensitivity analysis shows that HD-QIV has a 60% probability of being cost saving compared to aTIV.	
	Overall societal perspective result	Not applicable	
Authors conclusions	The HD-QIV in people ≥65 years is an influenza-prevention strategy that is at least cost effective, by reducing cases of influenza, GP visits, hospitalisations, deaths, and associated healthcare costs. It may become the dominant strategy when all the consequences of influenza (e.g. cardiorespiratory events) are considered in the assessment.		

Key: aTIV – adjuvanted trivalent influenza vaccine; CUA – cost-utility analysis; ED – emergency department; GP – general practitioner; HD-QIV – high-dose quadrivalent influenza vaccine; ICER – incremental cost-effectiveness ratio; LY – life year; QALY – quality-adjusted life yearquality-adjusted life year; rVE – relative vaccine effectiveness; Standard TIV – standard-dose trivalent influenza vaccine; VE – vaccine effectiveness.

General study characteristics	**Author name** **Year of publication** **DOI**	Ruiz-Aragón 2022 10.3390/vaccines10020176	
	Region or country	Spain	
	Type of economic evaluation	CUA	
	Population	≥65 years	
	Funding	Seqirus	
Model characteristics	**Model type**	Static decision-tree model	
	Perspective	Direct medical payer Societal	
	Time horizon	Costs and outcomes – one-year time horizon (one flu season) Productivity and QALY loss due to death – lifetime horizon	
	Comparator	HD-QIV	
	Discount rates	No discount for costs and outcomes in vaccination year 3% for productivity and QALY losses over lifetime horizon	
	Sensitivity analysis	Deterministic sensitivity analysis – one-way, PSA, scenario analysis – alternate rVE, alternate list prices for vaccine	
Intervention strategy	**Dosing schedule**	Not specified	
	Vaccine type (intervention)	aQIV	
	Age at vaccination	Not specified	
	Coverage rate	54.7%	
Model input parameters	**Efficacy/effectiveness**	Relative vaccine efficacy for HD-QIV vs standard QIV: 24% rVE of aTIV compared to HD-TIV: 4%	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ Primary care physician costs ▪ Emergency department (ED) costs ▪ Hospitalisation costs **Vaccine related costs** ▪ Vaccine acquisition costs **Indirect costs** ▪ Productivity loss due to direct illness ▪ Productivity losses for carers	**Measurement and valuation** **Direct costs** ▪ Primary care physician visit cost (€) ▪ ED visit cost (€) ▪ Cost of hospitalisation (€)– weighted average for relevant complications ▪ Cost of co-medication(€) – for primary care visit **Vaccine related costs** ▪ aQIV tender price (€) ▪ HD-QIV tender price (€) **Indirect costs** ▪ Productivity loss due to direct illness – discounted human capital approach ▪ Working days lost for outpatient and inpatient ▪ Life expectancy for ≥65 years population ▪ Probability of being employed (65-69 years, ≥75 years) ▪ Cost of productivity loss per hour (€) ▪ Probability of requiring care at home (65-69 years, ≥75 years)
	Effects included	**Type of effects** **Direct effects** ▪ Symptomatic cases ▪ Primary care visits ▪ ED visits ▪ Hospitalisations ▪ Deaths	**Measurement and valuation** **Direct effects** ▪ Rate of symptomatic cases per 100,000 aged ≥65 years ▪ Rate of primary care visits per 100,000 aged ≥65 years ▪ Rate of ED visits per 100,000 aged ≥65 years ▪ Rate of hospitalisations per 100,000 aged ≥65 years ▪ Rate of deaths per 100,000 aged ≥65 years conditional on hospitalisation **QALY loss per case** ▪ Baseline utility (age cohort ≥65 years) ▪ Disutility for inpatient treated influenza

			▪ Duration of disutility for inpatient treatment ▪ Disutility for outpatient treated influenza ▪ Duration of disutility for outpatient treatment ▪ Disutility of symptomatic case influenza ▪ Duration of disutility for symptomatic cases
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	HD-QIV is dominated by aQIV aQIV cost effective in 100% PSA iterations	
	Overall societal perspective result	HD-QIV is dominated by aQIV	
Authors conclusions	This analysis demonstrates that, largely driven by the economic benefits associated with vaccinating a large population with a less expensive vaccine with comparable effectiveness, aQIV is cost saving compared to HD-QIV from both a direct medical payer and societal perspective.		

Key: aQIV – adjuvanted quadrivalent influenza vaccine; CUA – cost-utility analysis; ED – emergency department; HD-QIV – high-dose quadrivalent influenza vaccine; HD-TIV – high-dose trivalent influenza vaccine; ICER – incremental cost-effectiveness ratio; NA – not applicable; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; rVE – relative vaccine effectiveness; Standard QIV – standard-dose quadrivalent influenza vaccine.

General study characteristics	**Author name** **Year of publication** **DOI**	Ruiz-Aragón 2023 10.3390/vaccines11020427	
	Region or country	Spain	
	Type of economic evaluation	CUA	
	Population	≥65 years	
	Funding	Seqirus	
Model characteristics	**Model type**	Static decision-tree model	
	Perspective	Not clearly specified – presumed societal	
	Time horizon	1-year time horizon Productivity and QALY losses due to premature death over lifetime horizon	
	Comparator	aQIV	
	Discount rates	No discount for costs or outcomes incurred in year of vaccination. 3% for productivity and QALY losses over lifetime horizon	
	Sensitivity analysis	Deterministic sensitivity analysis – one way, PSA, Scenario analysis	
Intervention strategy	**Dosing schedule**	Not specified	
	Vaccine type (intervention)	RIV4	
	Age at vaccination	Not specified	
	Coverage rate	69.4%	
Model input parameters	**Efficacy/effectiveness**	rVE of RIV4 vs aTIV preventing against influenza related inpatient stay: 10.7%	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ Primary care physician costs ▪ ED costs ▪ Hospitalisation costs **Vaccine related costs** ▪ Vaccine acquisition costs **Indirect costs** ▪ Productivity loss due to direct illness ▪ Productivity loss due to premature death ▪ Productivity losses for carers	**Measurement and valuation** **Direct costs** ▪ Primary care physician visit cost (€) ▪ Cost of co-medication (€) – for primary care visit per case ▪ ED visit cost in Euro ▪ Cost of hospitalisation in Euro – weighted average for relevant complications per event **Vaccine related costs** ▪ aQIV tender price (€) ▪ HD-QIV tender price (€) **Indirect costs** ▪ Productivity loss due to direct illness – discounted human capital approach ▪ Working days lost for outpatient and inpatient ▪ Life expectancy for ≥65 years population ▪ Probability of being employed (65-69 years, ≥75 years) ▪ Cost of productivity loss per hour (€) ▪ Probability of requiring care at home (65-69 years, ≥75 years) ▪ Productivity loss due to premature death
	Effects included	**Type of effects** **Direct effects** ▪ Symptomatic cases ▪ Primary care visits ▪ ED visits ▪ Hospitalisations ▪ Deaths	**Measurement and valuation** **Direct effects** ▪ Rate of symptomatic cases per 100,000 in ≥65 years ▪ Rate of primary care visits per 100,000 in ≥65 years ▪ Rate of ED visits per 100,000 in ≥65 years ▪ Rate of hospitalisations per 100,000 in ages ≥65 years ▪ Rate of deaths per 100,000 in ≥65 years

			QALY loss per case ▪ Baseline utility (age cohort ≥65 years) ▪ Disutility for inpatient treated influenza ▪ Duration of disutility for inpatient treatment ▪ Disutility for outpatient treated influenza ▪ Duration of disutility for outpatient treatment ▪ Disutility of symptomatic case influenza ▪ Duration of disutility for symptomatic cases ▪ QALY loss premature death
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	Not applicable	
	Overall societal perspective result	ICER for RIV4 versus aQIV was €101,612.41 per QALY gained. In PSA 99.7% of simulations for RIV4 were higher than the WTP curve. Scenario to meet the Spanish WTP threshold of €25,000 ICER – rVE would need to be 34.12% relatively more effective than aQIV. If the tender price were less than €16 per dose, then the cost effectiveness of RIV4 would meet the presumed WTP threshold of €25,000 per QALY gained	
Authors conclusions	Based on current tender prices in Spain and a conservative assumption that RIV4 is 10.7% relatively more effective than aQIV, findings suggest that RIV4 is not currently a cost-effective influenza vaccine option relative to aQIV for older persons living in Spain.		

Key: aQIV – adjuvanted quadrivalent influenza vaccine; aTIV – adjuvanted trivalent influenza vaccine; CUA – cost-utility analysis; ED – emergency department; HD-QIV – high-dose quadrivalent influenza vaccine; ICER – incremental cost effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; RIV4 – recombinant quadrivalent influenza vaccine; rVE – relative vaccine effectiveness; WTP – willingness-to-pay.

General study characteristics	**Author name** **Year of publication** **DOI**	Rumi 2021 10.33393/grhta.2021.2247	
	Region or country	Italy	
	Type of economic evaluation	CUA, CEA (Incremental cost per LY)	
	Population	Italian population ≥65 years	
	Funding	Sanofi	
Model characteristics	**Model type**	Static decision tree	
	Perspective	Healthcare payer (National Health Service in Italy)	
	Time horizon	One-year outcomes and costs LY and QALYs over a lifetime horizon	
	Comparator	Standard QIV	
	Discount rates	No discount on costs or outcomes incurred in vaccination year 3% for outcomes over lifetime horizon only	
	Sensitivity analysis	Deterministic sensitivity analysis – one way, PSA (Markov Chain Monte Carlo method)	
Intervention strategy	**Dosing schedule**	Not specified	
	Vaccine type (intervention)	HD-QIV	
	Age at vaccination	Not specified	
	Coverage rate	54.6%	
Model input parameters	**Efficacy/effectiveness**	HD-QIV relative vaccine efficacy compared to standard QIV: 24.2% VE in preventing cardiorespiratory hospitalisation: HD-QIV 18.2% (relative to standard QIV), standard QIV 14.6% (absolute)	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ OTC medication ▪ Prescription medication for flu ▪ Influenza related GP visit ▪ ED visit – flu related ▪ Hospitalisation **Vaccine related costs** ▪ Vaccine acquisition costs ▪ Vaccine administration costs	**Measurement and valuation** **Direct costs** ▪ Cost of OTC medication for influenza (€) ▪ Cost of prescription medication for influenza (€) ▪ Cost of influenza-related GP visit (€) ▪ Cost of ED visit – flu-related (€) ▪ Cost of hospitalisation as per cardiorespiratory DRGs (€) **Vaccine related costs** ▪ Standard QIV vaccine cost (€) ▪ HD-QIV vaccine cost (€) ▪ aTIV vaccine cost (€) ▪ Unit cost of administration (€)
	Effects included	**Type of effects** **Direct effects** ▪ Incidence of influenza ▪ Number of flu-related GP visits averted ▪ Number of flu-related ED visits averted ▪ Number of flu-related hospitalisations averted ▪ Influenza related mortality ▪ Life years lost due to premature influenza related death.	**Measurement and valuation** **Direct effects** ▪ Influenza virus attack rate ▪ Probability of having influenza ▪ Probability of accessing ED 65-74 years ▪ Probability of accessing the ED ≥75 years ▪ Probability of making a GP visit ▪ Hospitalisation rate per 100,000 for influenza and cardio-respiratory causes ▪ Percentage of hospitalisations during flu season ▪ Proportion of hospitalisations due to respiratory causes ▪ Excess mortality rate (per 100,000) ▪ Probability of death conditional on influenza 65-74 years ▪ Probability of death conditional on influenza ≥75 years ▪ Background mortality 65-75 years

			▪ Background mortality ≥75 years **QALY loss per case** *Incorporated as average QALY loss of influenza* ▪ Baseline utility (≥65 years) ▪ Disutility of influenza ▪ Disutility of hospitalisation (per episode) ▪ Duration of influenza ▪ Duration of hospitalisation
Economic results	**Type of summary ratio**	ICER (per QALY and LY gained)	
	Overall payer perspective result	HD-QIV dominates standard QIV for base case: hospitalisations for influenza and cardiorespiratory events (cheaper and more effective)	
	Overall societal perspective result	Not applicable	
Authors conclusions	Compared to the standard QIV, a dominant cost-effectiveness profile emerges, with a cost-effectiveness probability of 100% at a WTP level of €15,000 per QALY.		

Key: aTIV – adjuvanted trivalent influenza vaccine; CEA – cost-effectiveness analysis; CUA – cost-utility analysis; DRG – diagnosis related group; ED – emergency department; GP – general practitioner; HD-QIV – high-dose quadrivalent influenza vaccine; ICER – incremental cost-effectiveness ratio; LY – Life year; OTC – over-the-counter; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; Standard QIV – standard-dose quadrivalent influenza vaccine; VE – vaccine effectiveness ; WTP – willingness-to-pay.

General study characteristics	**Author name** **Year of publication** **DOI**	Sandmann 2022 10.1016/j.vaccine.2022.01.015	
	Region or country	England, France, Ireland, The Netherlands, Portugal, Scotland, Spain, and Navarre (Spain)	
	Type of economic evaluation	CUA	
	Population	Entire population (Note: Model includes vaccination strategies across the paediatric population and adults aged ≥65 years)	
	Funding	European Commission Horizon 2020 research and innovation programme (grant agreement No 634446); National Institute for Health Research Health Protection Research Unit (NIHR HPRU) and UK Health Security Agency (UKHSA) (grant HPRU-2012–10080).	
Model characteristics	**Model type**	Age-structured dynamic transmission model	
	Perspective	Healthcare	
	Time horizon	One year	
	Comparator	TIV for ≥65yr olds	
	Discount rates	0%; 3.0% for premature mortality due to influenza	
	Sensitivity analysis	Probabilistic	
Intervention strategy	**Dosing schedule**	1-dose	
	Vaccine type (intervention)	Five overall scenarios (with 27 different strategies): (i) switch those aged ≥65 years to enhanced TIV(i.e. aTIV or HD-TIV) (ii) switch those aged ≥65 years to QIV (iii) adopt mass paediatric (4-16 years) vaccination with TIV or QIV along with switch to enhanced TIV for those aged ≥65 years (iv) adopt mass paediatric (4-16 years) vaccination with TIV or QIV along with switch to QIV for those aged ≥65 years (v) combine the vaccination strategies for those aged ≥65 years and 4-16 years.	
	Age at vaccination	≥65 years and 4-16 years (paediatric)	
	Coverage rate	≥65 years old: varies from 50.9% for Portugal to 77.3% for Scotland 4-16 years: assumed 10%, 25%, 50% and 75% for each strategy under consideration.	
Model input parameters	**Efficacy/effectiveness**	Overall VE rates: provided by season, age group, and influenza subtype. VE by country and vaccine type not provided. rVE for enhanced TIV versus standard dose TIV: 24.2% VE for QIV against influenza B: TIV VE up-scaled using the relative ratio of the 95%CI of the TIV to the pooled central VE estimate of TIV with unchanged estimates from ECDC for the influenza virus (sub-) type A (estimate not provided)	
	Waning	Not applicable	
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - Outpatient (GP) consultations - Hospitalisation ▪ Vaccination costs - vaccine (by type) - vaccine administration **Indirect costs** ▪ N/R	**Measurement and valuation** **Direct costs** ▪ Medical costs - GP consultation cost (by country/region) - Hospitalisation cost (by country/region). Age-specific costs used for Navarro, the Netherlands, and Ireland but data not provided. ▪ Vaccination costs - vaccine cost (by type and country/region) - vaccine administration (by country/region) **Indirect costs** ▪ Not applicable
	Effects included	**Type of effects** **Direct effects** ▪ ILI cases ▪ Influenza-related outpatient visits (e.g. GP consultations) ▪ Influenza-related hospital admissions ▪ Influenza-related excess deaths **Indirect effects**	**Measurement and valuation** **Direct effects** ▪ ILI cases per 100,000 population (by age group and country/region) ▪ Influenza (sub-) type specific proportions of infected cases with ILI symptoms (by country/region) ▪ GP visits per 100,000 population (by age group and country/region)

		▪ Indirect protection for adults aged ≥65 years through introducing a mass paediatric influenza vaccination programme. ▪ Indirect protection for paediatric age groups through moving adults aged ≥65 years population to a different vaccine.	▪ Hospitalisations per 100,000 population (by age group and country/region) ▪ Excess mortality rate per 100,000 population (by age group and country/region) **QALYs** ▪ QALY loss inpatient (by country/region) ▪ QALY loss outpatient (by country/region) ▪ QALEs (by age group and country/region) **Indirect effects** ▪ Based on model outputs assessing changes in vaccination strategies.
Economic results	**Type of summary ratio**	ICER (per QALY gained)	
	Overall payer perspective result	At €15,000/QALY gained, adopting a mass paediatric vaccination programme achieves the highest probability of being cost effective, with or without moving adults aged ≥65 years to an enhanced TIV. Moving adults aged ≥65 years to an enhanced TIV plus adopting mass paediatric QIV programmes provides the highest mean net benefits in all settings at €25,000/QALY gained (with 10% mass paediatric uptake), €30,000/QALY gained (25% mass paediatric uptake), and €35,000/QALY gained (50% or 75% mass paediatric uptake). Due to diminishing rates of returns of the community effects, the probability that the optimal vaccination strategies are cost effective decreases as the paediatric mass vaccination coverage goes up.	
	Overall societal perspective result	Not applicable	
Authors conclusions	Given the direct and indirect protection, and depending on the vaccine prices, model results support a combination of having moved adults aged ≥65 years to an enhanced TIV and adopting universal paediatric vaccination programmes across the European settings.		

Key: CI – confidence interval; CUA – cost-utility analysis; ECDC – European Centre for Disease Prevention and Control; GP – general practitioner; ICER – incremental cost effectiveness ratio; ILI – influenza-like illness; NIHR HPRU - National Institute for Health Research Health Protection Research Unit; N/R – not reported; QALE – quality adjusted life expectancy; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccine; rVE – relative vaccine effectiveness; TIV – trivalent influenza vaccine; UKHSA – United Kingdom Health Security Agency; VE – vaccine effectiveness.

General study characteristics	**Author name** **Year of publication** **DOI**	Tavares 2022 10.3390/vaccines10081285	
	Region or country	Portugal	
	Type of economic evaluation	CUA	
	Population	≥65 years	
	Funding	Research/Government National Funding from FCT—Fundação para a Ciência e Tecnologia, Portugal, under the project UIDB/00006/2020.	
Model characteristics	**Model type**	Static decision tree	
	Perspective	National Health Service payer perspective	
	Time horizon	1-year	
	Comparator	TIV	
	Discount rates	Not applicable to one year time horizon.	
	Sensitivity analysis	Deterministic one-way sensitivity analysis, PSA, and scenario analysis - vaccination coverage rate, TIV effectiveness, QIV effectiveness, cost of QIV	
Intervention strategy	**Dosing schedule**	1-dose	
	Vaccine type (intervention)	QIV	
	Age at vaccination	≥65 years	
	Coverage rate	0.501	
Model input parameters	**Efficacy/effectiveness**	VE TIV=58% VE QIV=59.9%	
	Waning	Not applicable	
	Costs included	**<u>Type of cost</u>** **Direct costs** ▪ Medical - GP visit (influenza-related) - Cost of antiviral treatment - Hospitalisation - influenza-related - pneumonia - respiratory disease - heart disease - Death when hospitalised - influenza-related - pneumonia - respiratory disease - heart disease ▪ **Vaccine related costs** - Vaccine acquisition - Vaccine administration **Indirect costs** ▪ N/R	**<u>Measurement and valuation</u>** **Direct costs** ▪ Medical - Cost of GP visit (influenza-related) - Cost of antiviral treatment - considered to be included in the cost of hospitalisation and cost of death when hospitalised so only added to ILI pathways which did not result in hospitalisation - Cost of hospitalisation - influenza-related - pneumonia - respiratory disease - heart disease -Cost of death when hospitalised - influenza-related - pneumonia - respiratory disease - heart disease Vaccine related costs - Cost of TIV per dose - Cost of QIV per dose - Vaccine administration **Indirect costs** ▪ Not applicable
	Effects included	**<u>Type of effects</u>** **Direct effects** ▪ Medical	**<u>Measurement and valuation</u>** **Direct effects** ▪ Medical

		- GP visit (influenza-related) - Hospitalisation (influenza-related) - Death when hospitalised (influenza-related) - Hospitalisation (pneumonia) - Death when hospitalised (pneumonia) - Hospitalisation (respiratory disease) - Death when hospitalised (respiratory disease) - Hospitalisation (heart disease) - Death when hospitalised (heart disease) **Indirect effects** ▪ N/R	- Probability of influenza like illness - Probability of confirmed influenza - Probability of GP consultation - Probability of hospitalisation due to influenza - Probability of death when hospitalised due to influenza - Probability of hospitalisation due to pneumonia - Probability of death when hospitalised due to pneumonia - Probability of hospitalisation due to respiratory disease - Probability of death when hospitalised due to RD - Probability of hospitalisation due to Heart disease - Probability of death when hospitalised due to HD - Probability of death when no confirmed influenza **QALY loss per case** ▪ Utility loss - Disutility associated with ILI without influenza confirmation - Disutility associated with no hospitalised influenza - Disutility associated with hospitalisation due to influenza - Disutility associated with hospitalisation due to pneumonia - Disutility associated with hospitalisation due to respiratory disease - Disutility associated with hospitalisation due to heart disease - Utility associated with healthy population
Economic results	**Type of summary ratio**	ICER per QALY	
	Overall payer perspective result	€26,403,007 per QALY gained	
	Overall societal perspective result	Not applicable	
Authors conclusions	For the cost-effectiveness thresholds of €30,000/QALY or €34,000/QALY, QIV is not cost effective. Probabilistic sensitivity analysis enhanced the robustness of the base case results. The ICER is much higher than any possible ceiling ratio established by NHS. The need for a longer time horizon is here emphasised. Further investigation is required to fully understand the cost effectiveness of QIV versus TIV in Portugal. Future research might explore the cost effectiveness of influenza vaccination for the entire population, and not only focusing on adults aged ≥65 years population.		

Key: CUA – cost-utility analysis; FCT – Fundação para a Ciência e Tecnologia; GP – general practitioner; HD – heart disease; ICER – incremental cost-effectiveness ratio; ILI – influenza-like illness; NHS – national health service; NR – not reported; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life yearquality-adjusted life year; QIV – quadrivalent influenza vaccine; RD – respiratory disease; TIV – trivalent influenza vaccine; VE – vaccine effectiveness.

A6.1 Differential equations

Rate of change in group 1 (0 to 17yr olds)

```
dS1 <- - v_cov_1 * m_cov_1 * (1 - p_vf) * v_eff_1 * S1 - v_cov_1 * m_cov_1 * p_vf * S1 - v_cov_1 * m_cov_1 * (1 - p_vf) * (1 - v_eff_1) * S1 - lambda_1 * S1 - mu_ac_1 * S1 - mu_in_1 * S1
dE1 <- lambda_1 * S1 + lambda_1 * VF1 - sigma * E1 - mu_ac_1 * E1 - mu_in_1 * E1
dI1 <- sigma * E1 - gamma * I1 - mu_ac_1 * I1 - mu_in_1 * I1
dR1 <- gamma * I1 - mu_ac_1 * R1
dVP1 <- v_cov_1 * m_cov_1 * (1 - p_vf) * v_eff_1 * S1 - mu_ac_1 * VP1
dVF1 <- v_cov_1 * m_cov_1 * p_vf * S1 - lambda_1 * VF1 - mu_ac_1 * VF1 - mu_in_1 * VF1
dVS1 <- v_cov_1 * m_cov_1 * (1 - p_vf) * (1 - v_eff_1) * S1 - vlambda_1 * VS1 - mu_ac_1 * VS1 - mu_in_1 * VS1
dVE1 <- vlambda_1 * VS1 - sigma * VE1 - mu_ac_1 * VE1 - mu_in_1 * VE1
dVI1 <- sigma * VE1 - gamma * VI1 - mu_ac_1 * VI1 - mu_in_1 * VI1
dVR1 <- gamma * VI1 - mu_ac_1 * VR1
dDAC1 <- mu_ac_1 * S1 + mu_ac_1 * E1 + mu_ac_1 * I1 + mu_ac_1 * R1
dDIN1 <- mu_in_1 * S1 + mu_in_1 * E1 + mu_in_1 * I1
dVDAC1 <- mu_ac_1 * VP1 + mu_ac_1 * VF1 + mu_ac_1 * VS1 + mu_ac_1 * VE1 + mu_ac_1 * VI1 + mu_ac_1 * VR1
dVDIN1 <- mu_in_1 * VF1 + mu_in_1 * VS1 + mu_in_1 * VE1 + mu_in_1 * VI1
```

Rate of change in group 2 (17 to 49yr olds):

```
dS2 <- - v_cov_2 * m_cov_2 * (1 - p_vf) * v_eff_2 * S2 - v_cov_2 * m_cov_2 * p_vf * S2 - v_cov_2 * m_cov_2 * (1 - p_vf) * (1 - v_eff_2) * S2 - lambda_2 * S2 - mu_ac_2 * S2 - mu_in_2 * S2
dE2 <- lambda_2 * S2 + lambda_2 * VF2 - sigma * E2 - mu_ac_2 * E2 - mu_in_2 * E2
dI2 <- sigma * E2 - gamma * I2 - mu_ac_2 * I2 - mu_in_2 * I2
dR2 <- gamma * I2 - mu_ac_2 * R2
dVP2 <- v_cov_2 * m_cov_2 * (1 - p_vf) * v_eff_2 * S2 - mu_ac_2 * VP2
dVF2 <- v_cov_2 * m_cov_2 * p_vf * S2 - lambda_2 * VF2 - mu_ac_2 * VF2 - mu_in_2 * VF2
dVS2 <- v_cov_2 * m_cov_2 * (1 - p_vf) * (1 - v_eff_2) * S2 - vlambda_2 * VS2 - mu_ac_2 * VS2 - mu_in_2 * VS2
dVE2 <- vlambda_2 * VS2 - sigma * VE2 - mu_ac_2 * VE2 - mu_in_2 * VE2
dVI2 <- sigma * VE2 - gamma * VI2 - mu_ac_2 * VI2 - mu_in_2 * VI2
dVR2 <- gamma * VI2 - mu_ac_2 * VR2
dDAC2 <- mu_ac_2 * S2 + mu_ac_2 * E2 + mu_ac_2 * I2 + mu_ac_2 * R2
dDIN2 <- mu_in_2 * S2 + mu_in_2 * E2 + mu_in_2 * I2
dVDAC2 <- mu_ac_2 * VP2 + mu_ac_2 * VF2 + mu_ac_2 * VS2 + mu_ac_2 * VE2 + mu_ac_2 * VI2 + mu_ac_2 * VR2
dVDIN2 <- mu_in_2 * VF1 + mu_in_2 * VS2 + mu_in_2 * VE2 + mu_in_2 * VI2
```

Rate of change in group 3 (50 to 64yr olds):

```
dS3 <- - v_cov_3 * m_cov_3 * (1 - p_vf) * v_eff_2 * S3 - v_cov_3 * m_cov_3 * p_vf * S3 - v_cov_3 * m_cov_3 * (1 - p_vf) * (1 - v_eff_2) * S3 - lambda_3 * S3 - mu_ac_3 * S3 - mu_in_3 * S3
dE3 <- lambda_3 * S3 + lambda_3 * VF3 - sigma * E3 - mu_ac_3 * E3 - mu_in_3 * E3
dI3 <- sigma * E3 - gamma * I3 - mu_ac_3 * I3 - mu_in_3 * I3
dR3 <- gamma * I3 - mu_ac_3 * R3
dVP3 <- v_cov_3 * m_cov_3 * (1 - p_vf) * v_eff_2 * S3 - mu_ac_3 * VP3
dVF3 <- v_cov_3 * m_cov_3 * p_vf * S3 - lambda_3 * VF3 - mu_ac_3 * VF3 - mu_in_3 * VF3
dVS3 <- v_cov_3 * m_cov_3 * (1 - p_vf) * (1 - v_eff_2) * S3 - vlambda_3 * VS3 - mu_ac_3 * VS3 - mu_in_3 * VS3
dVE3 <- vlambda_3 * VS3 - sigma * VE3 - mu_ac_3 * VE3 - mu_in_3 * VE3
dVI3 <- sigma * VE3 - gamma * VI3 - mu_ac_3 * VI3 - mu_in_3 * VI3
```

```
  dVR3  <- gamma * VI3 - mu_ac_3 * VR3
  dDAC3   <- mu_ac_3 * S3 + mu_ac_3 * E3 + mu_ac_3 * I3 + mu_ac_3 * R3
  dDIN3   <- mu_in_3 * S3 + mu_in_3 * E3 + mu_in_3 * I3
  dVDAC3  <- mu_ac_3 * VP3 + mu_ac_3 * VF3 + mu_ac_3 * VS3 + mu_ac_3 * VE3 + mu_ac_3 *
VI3 + mu_ac_3 * VR3
  dVDIN3  <- mu_in_3 * VF3 + mu_in_3 * VS3 + mu_in_3 * VE3 + mu_in_3 * VI3
```

Rate of change in group 4 (65 to 69yr olds):

```
  dS4 <- - v_cov_4 * m_cov_4 * (1 - p_vf) * v_eff_4 * S4 - v_cov_4 * m_cov_4 * p_vf * S4 -
v_cov_4 * m_cov_4 * (1 - p_vf) * (1 - v_eff_4) * S4 - lambda_4 * S4 - mu_ac_4 * S4 - mu_in_4 *
S4
  dE4 <- lambda_4 * S4 + lambda_4 * VF4 - sigma * E4 - mu_ac_4 * E4 - mu_in_4 * E4
  dI4 <- sigma * E4 - gamma * I4 - mu_ac_4 * I4 - mu_in_4 * I4
  dR4 <- gamma * I4 - mu_ac_4 * R4
  dVP4 <- v_cov_4 * m_cov_4 * (1 - p_vf) * v_eff_4 * S4 - mu_ac_4 * VP4
  dVF4 <- v_cov_4 * m_cov_4 * p_vf * S4 - lambda_4 * VF4 - mu_ac_4 * VF4 - mu_in_4 * VF4
  dVS4  <- v_cov_4 * m_cov_4 * (1 - p_vf) * (1 - v_eff_4) * S4 - vlambda_4 * VS4 - mu_ac_4 *
VS4 - mu_in_4 * VS4
  dVE4  <- vlambda_4 * VS4 - sigma * VE4 - mu_ac_4 * VE4 - mu_in_4 * VE4
  dVI4  <- sigma * VE4 - gamma * VI4 - mu_ac_4 * VI4 - mu_in_4 * VI4
  dVR4  <- gamma * VI4 - mu_ac_4 * VR4
  dDAC4   <- mu_ac_4 * S4 + mu_ac_4 * E4 + mu_ac_4 * I4 + mu_ac_4 * R4
  dDIN4   <- mu_in_4 * S4 + mu_in_4 * E4 + mu_in_4 * I4
  dVDAC4  <- mu_ac_4 * VP4 + mu_ac_4 * VF4 + mu_ac_4 * VS4 + mu_ac_4 * VE4 + mu_ac_4 *
VI4 + mu_ac_4 * VR4
  dVDIN4  <- mu_in_4 * VF4 + mu_in_4 * VS4 + mu_in_4 * VE4 + mu_in_4 * VI4
```

Rate of change in group 5 (70 to 74yr olds):

```
  dS5 <- - v_cov_5 * m_cov_5 * (1 - p_vf) * v_eff_4 * S5 - v_cov_5 * m_cov_5 * p_vf * S5 -
v_cov_5 * m_cov_5 * (1 - p_vf) * (1 - v_eff_4) * S5 - lambda_5 * S5 - mu_ac_5 * S5 - mu_in_5 *
S5
  dE5 <- lambda_5 * S5 + lambda_5 * VF5 - sigma * E5 - mu_ac_5 * E5 - mu_in_5 * E5
  dI5 <- sigma * E5 - gamma * I5 - mu_ac_5 * I5 - mu_in_5 * I5
  dR5 <- gamma * I5 - mu_ac_5 * R5
  dVP5 <- v_cov_5 * m_cov_5 * (1 - p_vf) * v_eff_4 * S5 - mu_ac_5 * VP5
  dVF5 <- v_cov_5 * m_cov_5 * p_vf * S5 - lambda_5 * VF5 - mu_ac_5 * VF5 - mu_in_5 * VF5
  dVS5  <- v_cov_5 * m_cov_5 * (1 - p_vf) * (1 - v_eff_4) * S5 - vlambda_5 * VS5 - mu_ac_5 *
VS5 - mu_in_5 * VS5
  dVE5  <- vlambda_5 * VS5 - sigma * VE5 - mu_ac_5 * VE5 - mu_in_5 * VE5
  dVI5  <- sigma * VE5 - gamma * VI5 - mu_ac_5 * VI5 - mu_in_5 * VI5
  dVR5  <- gamma * VI5 - mu_ac_5 * VR5
  dDAC5   <- mu_ac_5 * S5 + mu_ac_5 * E5 + mu_ac_5 * I5 + mu_ac_5 * R5
  dDIN5   <- mu_in_5 * S5 + mu_in_5 * E5 + mu_in_5 * I5
  dVDAC5  <- mu_ac_5 * VP5 + mu_ac_5 * VF5 + mu_ac_5 * VS5 + mu_ac_5 * VE5 + mu_ac_5 *
VI5 + mu_ac_5 * VR5
  dVDIN5  <- mu_in_5 * VF5 + mu_in_5 * VS5 + mu_in_5 * VE5 + mu_in_5 * VI5
```

Rate of change in group 6: (75 to 79yr olds)

```
  dS6 <- - v_cov_6 * m_cov_6 * (1 - p_vf) * v_eff_4 * S6 - v_cov_6 * m_cov_6 * p_vf * S6 -
v_cov_6 * m_cov_6 * (1 - p_vf) * (1 - v_eff_4) * S6 - lambda_6 * S6 - mu_ac_6 * S6 - mu_in_6 *
S6
  dE6 <- lambda_6 * S6 + lambda_6 * VF6 - sigma * E6 - mu_ac_6 * E6 - mu_in_6 * E6
  dI6 <- sigma * E6 - gamma * I6 - mu_ac_6 * I6 - mu_in_6 * I6
  dR6 <- gamma * I6 - mu_ac_6 * R6
  dVP6 <- v_cov_6 * m_cov_6 * (1 - p_vf) * v_eff_4 * S6 - mu_ac_6 * VP6
  dVF6 <- v_cov_6 * m_cov_6 * p_vf * S6 - lambda_6 * VF6 - mu_ac_6 * VF6 - mu_in_6 * VF6
```

```
  dVS6  <- v_cov_6 * m_cov_6 * (1 - p_vf) * (1 - v_eff_4) * S6 - vlambda_6 * VS6 - mu_ac_6 *
VS6 - mu_in_6 * VS6
  dVE6  <- vlambda_6 * VS6 - sigma * VE6 - mu_ac_6 * VE6 - mu_in_6 * VE6
  dVI6  <- sigma * VE6 - gamma * VI6 - mu_ac_6 * VI6 - mu_in_6 * VI6
  dVR6  <- gamma * VI6 - mu_ac_6 * VR6
  dDAC6   <- mu_ac_6 * S6 + mu_ac_6 * E6 + mu_ac_6 * I6 + mu_ac_6 * R6
  dDIN6   <- mu_in_6 * S6 + mu_in_6 * E6 + mu_in_6 * I6
  dVDAC6  <- mu_ac_6 * VP6 + mu_ac_6 * VF6 + mu_ac_6 * VS6 + mu_ac_6 * VE6 + mu_ac_6 *
VI6 + mu_ac_6 * VR6
  dVDIN6  <- mu_in_6 * VF6 + mu_in_6 * VS6 + mu_in_6 * VE6 + mu_in_6 * VI6
```

Key for health states:

DAC – dead due to all-causes other than influenza; DIN – dead due to influenza; E – exposed; I – infectious; R – recovered; S – susceptible; VDAC – vaccinated and dead due to all causes other than influenza; VDIN – vaccinated and dead due to influenza; VE – vaccinated exposed; VF – vaccinated failed; VI – vaccinated infectious; VP – vaccinated protected; VR – vaccinated recovered; VS – vaccinated susceptible.

Key for rates:

gamma – recovery rate from influenza; lambda – force of infection rate; mu_ac – all-cause mortality rate; mu_in – influenza-related mortality rate; sigma – latency rate; m_cov – multiplier for vaccination coverage rate; p_vf – probability of vaccine failure; r_v_eff – relative vaccine effectiveness of enhanced influenza vaccine (versus standard influenza vaccine); v_cov – vaccination coverage rate; v_eff – vaccine effectiveness rate.

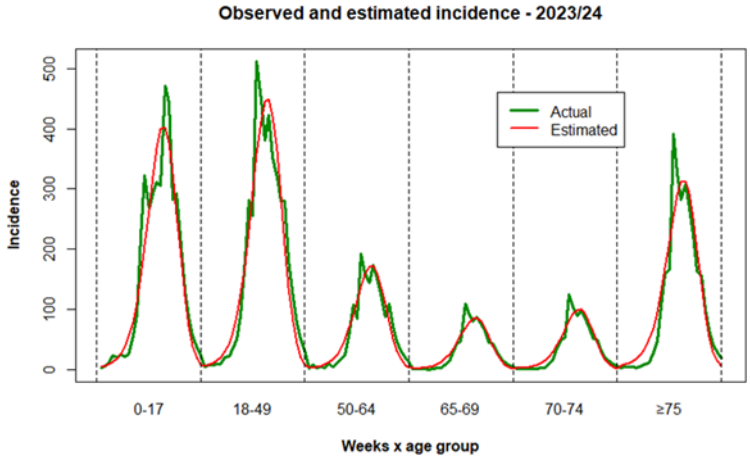
A6.2 Contact matrix – average number of daily contacts by age

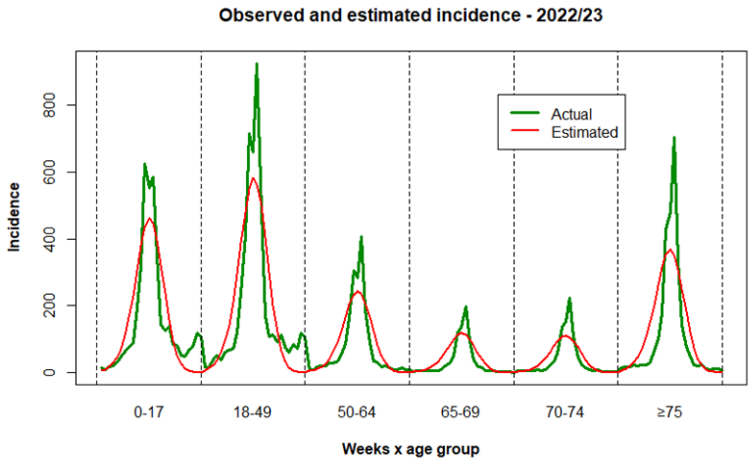
Age group (years)	0-17	18-49	50-64	65-69	70-74	≥75
0-17	7.813187	4.640110	0.865385	0.118132	0.076923	0.071429
18-49	2.530864	7.108642	1.558025	0.207407	0.143210	0.197531
50-64	1.172043	4.790323	2.311828	0.284946	0.220430	0.354839
65-69	1.296296	4.444444	2.259259	0.703704	0.333333	0.407407
70-74	1.090909	3.090909	1.363636	0.818182	0.590909	0.863636
≥75	0.857143	1.857143	2.000000	0.000000	0.142857	0.857143

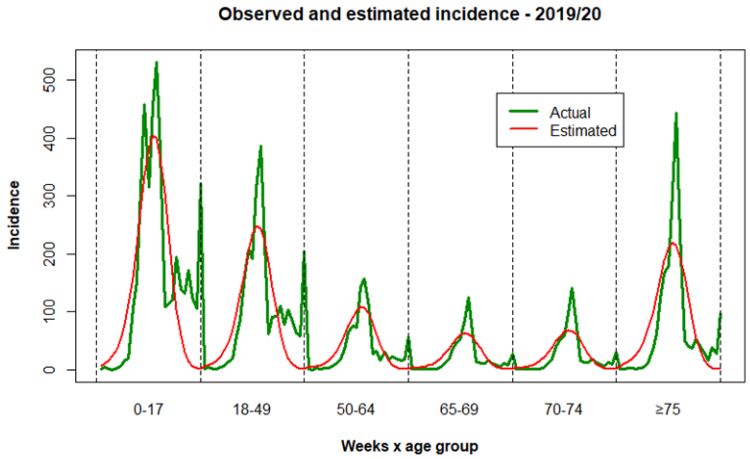
Source: Mossong et al.[285]

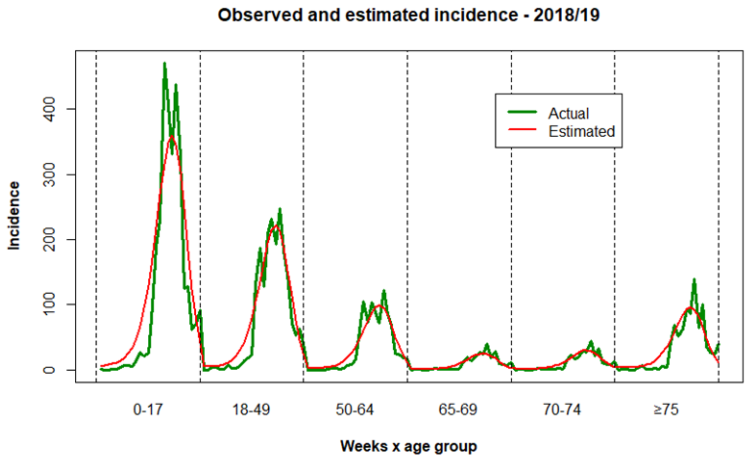
A6.3 Observed and estimated (from epidemiological model) incidence (number of cases) of notified influenza cases over five influenza seasons in Ireland

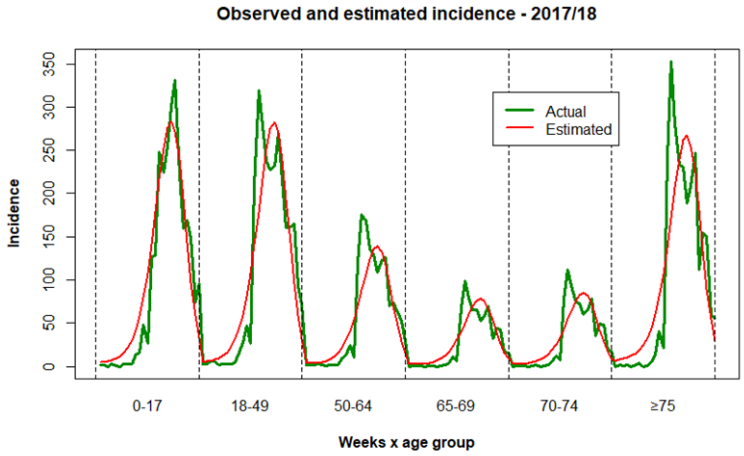
Influenza Season	Observed incidence[†]	Estimated incidence
2017/18	10,987	11,240
2018/19	7,305	8,055
2019/20	11,034	10,529
2022/23	15,472	16,564
2023/24	14,826	14,845




Observed and estimated incidence - 2022/23
Actual
Estimated
Incidence
0
200
400
600
800
0-17
18-49
50-64
65-69
70-74
≥75
Weeks x age group


Observed and estimated incidence - 2019/20
Actual
Estimated
Incidence
0
100
200
300
400
500
0-17
18-49
50-64
65-69
70-74
≥75
Weeks x age group


Observed and estimated incidence - 2018/19
Actual
Estimated
Incidence
0
100
200
300
400
0-17
18-49
50-64
65-69
70-74
≥75
Weeks x age group


Observed and estimated incidence - 2017/18
Actual
Estimated
Incidence
0
50
100
150
200
250
300
350
0-17
18-49
50-64
65-69
70-74
≥75
Weeks x age group

A6.4 Economic model input parameters

Parameter Description	Base case value	Lower Range	Upper Range	Distribution	Source
Resource use parameters					
Probability GP visit for influenza					
Probability GP visit for influenza_age group 1	1.00	1.00	1.00	Fixed	Assumed - given only notified cases modelled
Probability GP visit for influenza_age group 2	1.00	1.00	1.00	Fixed	
Probability GP visit for influenza_age group 3	1.00	1.00	1.00	Fixed	
Probability GP visit for influenza_age group 4	1.00	1.00	1.00	Fixed	
Probability GP visit for influenza_age group 5	1.00	1.00	1.00	Fixed	
Probability GP visit for influenza_age group 6	1.00	1.00	1.00	Fixed	
Frequency of GP visit for influenza					
Frequency of GP visit for influenza_age group 1	1.13	1.07	1.19	Gamma	Meier et al. 2020[300]
Frequency of GP visit for influenza_age group 2	1.12	1.06	1.18	Gamma	
Frequency of GP visit for influenza_age group 3	1.15	1.09	1.21	Gamma	
Frequency of GP visit for influenza_age group 4	1.22	1.16	1.28	Gamma	
Frequency of GP visit for influenza_age group 5	1.22	1.16	1.28	Gamma	
Frequency of GP visit for influenza_age group 6	1.22	1.16	1.28	Gamma	
Probability prescription medication prescribed by GP for influenza					
Probability medication prescribed by GP for influenza_age group 1	0.551	0.440	0.66	Beta	Ehlken et al. 2015[301]
Probability medication prescribed by GP for influenza_age group 2	0.481	0.385	0.58	Beta	
Probability medication prescribed by GP for influenza_age group 3	0.481	0.385	0.58	Beta	
Probability medication prescribed by GP for influenza_age group 4	0.481	0.385	0.58	Beta	
Probability medication prescribed by GP for influenza_age group 5	0.481	0.385	0.58	Beta	
Probability medication prescribed by GP for influenza_age group 6	0.481	0.385	0.58	Beta	
Probability GP visit card					
Probability GP visit card_age group 1	0.292	0.292	0.29	Fixed	Primary Care Reimbursement Service[299]
Probability GP visit card_age group 2	0.032	0.032	0.03	Fixed	
Probability GP visit card_age group 3	0.030	0.030	0.03	Fixed	
Probability GP visit card_age group 4	0.031	0.031	0.03	Fixed	
Probability GP visit card_age group 5	0.358	0.358	0.36	Fixed	
Probability GP visit card_age group 6	0.228	0.228	0.23	Fixed	
Probability medical card					
Probability medical card_age group 1	0.288	0.288	0.29	Fixed	Primary Care Reimbursement Service[299]
Probability medical card_age group 2	0.215	0.215	0.22	Fixed	

Parameter Description	Base case value	Lower Range	Upper Range	Distribution	Source
Probability medical card_age group 3	0.290	0.290	0.29	Fixed	
Probability medical card_age group 4	0.387	0.387	0.39	Fixed	
Probability medical card_age group 5	0.569	0.569	0.57	Fixed	
Probability medical card_age group 6	0.772	0.772	0.77	Fixed	
Probability OTC medication recommended for influenza					
Probability OTC medication recommended for influenza_age group 1	1.00	1.00	1.00	Fixed	Assumed
Probability OTC medication recommended for influenza_age group 2	1.00	1.00	1.00	Fixed	
Probability OTC medication recommended for influenza_age group 3	1.00	1.00	1.00	Fixed	
Probability OTC medication recommended for influenza_age group 4	1.00	1.00	1.00	Fixed	
Probability OTC medication recommended for influenza_age group 5	1.00	1.00	1.00	Fixed	
Probability OTC medication recommended for influenza_age group 6	1.00	1.00	1.00	Fixed	
Probability hospitalisation for influenza					
Probability hospitalisation (severe influenza)_age group 1	0.276	0.143	0.434	Beta	Hospital In-Patient Enquiry (HIPE) System Discharge Data and Health Protection Surveillance Centre (as outlined in Chapter 3)
Probability hospitalisation (severe influenza)_age group 2	0.175	0.081	0.295	Beta	
Probability hospitalisation (severe influenza)_age group 3	0.347	0.186	0.528	Beta	
Probability hospitalisation (severe influenza)_age group 4	0.384	0.185	0.606	Beta	
Probability hospitalisation (severe influenza)_age group 5	0.384	0.185	0.606	Beta	
Probability hospitalisation (severe influenza)_age group 6	0.384	0.215	0.569	Beta	
Cost parameters					
Direct medical costs - influenza					
Cost of GP visit for varicella_public	€51.37	€41.61	€62.14	Gamma	Smith et al. 2021[302]
Cost of GP visit for varicella_private	€55.84	€45.23	€67.55	Gamma	
Cost of prescription medication for influenza public_age group 1	€9.46	€7.66	€11.44	Gamma	HSE Prescribing guidelines - Recommended treatment courses for URTI and LRTI presenting in primary care[303] Primary Care Reimbursement Service[352]
Cost of prescription medication for influenza public_age group 2	€8.96	€7.26	€10.84	Gamma	
Cost of prescription medication for influenza public_age group 3	€8.96	€7.26	€10.84	Gamma	
Cost of prescription medication for influenza public_age group 4	€8.96	€7.26	€10.84	Gamma	
Cost of prescription medication for influenza public_age group 5	€8.96	€7.26	€10.84	Gamma	
Cost of prescription medication for influenza public_age group 6	€8.96	€7.26	€10.84	Gamma	
Cost of prescription medication for influenza private_age group 1	€12.78	€10.35	€15.46	Gamma	HSE Prescribing guidelines - Recommended treatment courses for URTI and LRTI presenting in primary care[303] Primary Care Reimbursement Service[352]
Cost of prescription medication for influenza private_age group 2	€12.03	€9.74	€14.55	Gamma	
Cost of prescription medication for influenza private_age group 3	€12.03	€9.74	€14.55	Gamma	
Cost of prescription medication for influenza private_age group 4	€12.03	€9.74	€14.55	Gamma	
Cost of prescription medication for influenza private_age group 5	€12.03	€9.74	€14.55	Gamma	
Cost of prescription medication for influenza private_age group 6	€12.03	€9.74	€14.55	Gamma	

Parameter Description	Base case value	Lower Range	Upper Range	Distribution	Source
Cost of OTC medication for influenza_age group 1	€21.00	€17.01	€25.40	Gamma	HSE Prescribing guidelines - Recommended treatment courses for URTI and LRTI presenting in primary care[303]
Cost of OTC medication for influenza_age group 2	€33.00	€26.73	€39.92	Gamma	
Cost of OTC medication for influenza_age group 3	€33.00	€26.73	€39.92	Gamma	
Cost of OTC medication for influenza_age group 4	€33.00	€26.73	€39.92	Gamma	
Cost of OTC medication for influenza_age group 5	€33.00	€26.73	€39.92	Gamma	
Cost of OTC medication for influenza_age group 6	€33.00	€26.73	€39.92	Gamma	
Cost of hospitalisation for severe influenza_age group 1	€4,618	€3,741	€5,586	Gamma	Healthcare Pricing Office and Hospital In-Patient Enquiry (HIPE) System Discharge Data and Health Protection Surveillance Centre (as outlined in Chapter 3)
Cost of hospitalisation for severe influenza_age group 2	€4,609	€3,733	€5,575	Gamma	
Cost of hospitalisation for severe influenza_age group 3	€4,841	€3,921	€5,855	Gamma	
Cost of hospitalisation for severe influenza_age group 4	€5,031	€4,075	€6,086	Gamma	
Cost of hospitalisation for severe influenza_age group 5	€5,231	€4,237	€6,328	Gamma	
Cost of hospitalisation for severe influenza_age group 6	€5,479	€4,438	€6,627	Gamma	
Indirect costs - influenza - probability of productivity loss					
Probability of productivity loss for those with influenza_age group 1	0.05	0.05	0.05	Fixed	Central Statistics Office[307] REF:https://www.cso.ie/en/releasesandpublications/ep/plfs/labourforcesurveyquarter22023/employment/
Probability of productivity loss for those with influenza_age group 2	0.79	0.79	0.79	Fixed	
Probability of productivity loss for those with influenza_age group 3	0.73	0.73	0.73	Fixed	
Probability of productivity loss for those with influenza_age group 4	0.27	0.27	0.27	Fixed	
Probability of productivity loss for those with influenza_age group 5	0.17	0.17	0.17	Fixed	
Probability of productivity loss for those with influenza_age group 6	0.05	0.05	0.05	Fixed	
Probability of productivity loss for carers of those with influenza_age group 1	0.72	0.5622	0.85	Beta	EU-SILC (EU statistics on income and living conditions)[353]
Indirect costs - productivity loss (1 day) for influenza					
Productivity loss (1 day) for those with influenza_age group 1	€70.77	€57.33	€85.61	Gamma	Central Statistics Office[307]
Productivity loss (1 day) for those with influenza_age group 2	€143.18	€115.98	€173.20	Gamma	
Productivity loss (1 day) for those with influenza_age group 3	€149.35	€120.98	€180.66	Gamma	
Productivity loss (1 day) for those with influenza_age group 4	€124.09	€100.52	€150.11	Gamma	
Productivity loss (1 day) for those with influenza_age group 5	€124.09	€100.52	€150.11	Gamma	
Productivity loss (1 day) for those with influenza_age group 6	€124.09	€100.52	€150.11	Gamma	
Productivity loss (1 day) for caregivers of those with influenza_age group 1	€143.18	€115.98	€173.20	Gamma	Central Statistics Office[307]
Work days lost due to illness					
Work days lost for those with non-severe influenza_age group 1	5	4	6	Gamma	Assumed
Work days lost for those with non-severe influenza_age group 2	5	4	6	Gamma	
Work days lost for those with non-severe influenza_age group 3	5	4	6	Gamma	

Parameter Description	Base case value	Lower Range	Upper Range	Distribution	Source
Work days lost for those with non-severe influenza_age group 4	5	4	6	Gamma	
Work days lost for those with non-severe influenza_age group 5	5	4	6	Gamma	
Work days lost for those with non-severe influenza_age group 6	5	4	6	Gamma	
***Note: work days lost for those with non-severe influenza equals the number of days (n=7) with quality of life impact less 2 weekend days.					
***Note: work days lost for those with severe (hospitalised) influenza equals the number of days lost for non-severe influenza (n=5) plus the average length of stay in hospital.					
Work days lost for caregivers of those with non-severe influenza	5	4	6.00	Gamma	Assumed
***Note: work days lost for caregivers of those with non-severe influenza equals the number of work days lost for patients with non-severe illness.					
***Note: work days lost for caregivers of those with severe (hospitalised) influenza equals the number of work days lost for caregivers of those with non-severe illness plus the average length of stay in hospital.					
Length of stay - hospitalised case of influenza					
Average length of stay hospitalised influenza case_ age group 1	2.7	2.2	3.3	Gamma	Hospital In-Patient Enquiry (HIPE) System Discharge Data and Health Protection Surveillance Centre (as outlined in Chapter 3)
Average length of stay hospitalised influenza case_ age group 2	3.1	2.5	3.8	Gamma	
Average length of stay hospitalised influenza case_ age group 3	5.8	4.7	7.1	Gamma	
Average length of stay hospitalised influenza case_ age group 4	7.3	5.9	8.8	Gamma	
Average length of stay hospitalised influenza case_ age group 5	9.1	7.4	11.0	Gamma	
Average length of stay hospitalised influenza case_ age group 6	12.2	9.9	14.8	Gamma	
Infected days					
Number of days in infected state for influenza (from epidemiological model)	2	2	2.00	Fixed	EPI model
Quality of life parameters					
Baseline utilities					
Baseline utility_age group 1	0.9800	0.9800	0.9800	Fixed	Hobbins et al. 2018[296]
Baseline utility_age group 2	0.9477	0.9477	0.9477	Fixed	
Baseline utility_age group 3	0.9031	0.9031	0.9031	Fixed	
Baseline utility_age group 4	0.8790	0.8790	0.8790	Fixed	
Baseline utility_age group 5	0.8790	0.8790	0.8790	Fixed	
Baseline utility_age group 6	0.8410	0.8410	0.8410	Fixed	
Influenza utilities					
Utility_flu_age group 1	0.5700	0.4568	0.6796	Beta	Hollmann et al. 2013[297]
Utility_flu_age group 2	0.4878	0.3926	0.5834	Beta	
Utility_flu_age group 3	0.5431	0.4360	0.6483	Beta	
Utility_flu_age group 4	0.5590	0.4483	0.6668	Beta	
Utility_flu_age group 5	0.5590	0.4483	0.6668	Beta	

Parameter Description	Base case value	Lower Range	Upper Range	Distribution	Source
Utility_flu_age group 6	0.5210	0.4187	0.6224	Beta	
Utility_hosp_flu_age group 1	0.4400	0.3548	0.5270	Beta	Hollmann et al. 2013[297]
Utility_hosp_flu_age group 2	0.3533	0.2857	0.4240	Beta	
Utility_hosp_flu_age group 3	0.3231	0.2615	0.3880	Beta	
Utility_hosp_flu_age group 4	0.3190	0.2582	0.3831	Beta	
Utility_hosp_flu_age group 5	0.3190	0.2582	0.3831	Beta	
Utility_hosp_flu_age group 6	0.2810	0.2276	0.3376	Beta	
Number of days of QALY loss_all	7	6	8.5	Gamma	Hollmann et al. 2013[297]
Other parameters					
Vaccine parameters					
Cost of standard IIV - adults	€10.99	10.99	10.99	Fixed	Assumed
Relative cost of aIIV (versus standard IIV)	1.5	1.2	1.7	Log Normal	Estimated from Chapter 5
Relative cost of HD-IIV (versus standard IIV)	3.3	2.4	4.4	Log Normal	Estimated from Chapter 5
Relative risk hospitalisation_aIIV (versus standard IIV) (1- rVE)	0.408	0.19	0.85	Log Normal	Chapter 4 Clinical Effectiveness & Safety
QALY loss vaccination systemic adverse events	0.0010	0.000647	0.00143	Beta	Assumed
Relative risk 'vomitting' systemic adverse event_aIIV (versus standard IIV)	1.48	1.10	1.99	Log Normal	Chapter 4 Clinical Effectiveness & Safety
Relative risk 'combined' systemic adverse event_HD_IIV (versus standard IIV)	1.19	1.09	1.30	Log Normal	Chapter 4 Clinical Effectiveness & Safety
VAT	23.0%	23.0%	0.23	Fixed	Revenue[354]
Discount rate_costs	4.0%	3.3%	4.8%	Beta	Health Information and Quality Authority[273]
Vaccination programme parameters					
Eligible population_age group 1	1,225,738	1,225,738	1,225,738	Fixed	Central Statistics Office[286]
Eligible population_age group 2	2,293,575	2,293,575	2,293,575	Fixed	
Eligible population_age group 3	956,003	956,003	956,003	Fixed	
Eligible population_age group 4	244,829	244,829	244,829	Fixed	
Eligible population_age group 5	210,545	210,545	210,545	Fixed	
Eligible population_age group 6	350,922	350,922	350,922	Fixed	
Vaccination coverage_age group 4	62.3%	62.3%	62.3%	Fixed	Health Protection Surveillance Centre[276]
Vaccination coverage_age group 5	75.8%	75.8%	75.8%	Fixed	
Vaccination coverage_age group 6	87.1%	87.1%	87.1%	Fixed	
Vaccinated population_age group 4	152,532	152,532	152,532	Fixed	Calculated
Vaccinated population_age group 5	159,571	159,571	159,571	Fixed	Calculated
Vaccinated population_age group 6	305,699	305,699	305,699	Fixed	Calculated

Parameter Description	Base case value	Lower Range	Upper Range	Distribution	Source
Demographic parameters					
Life expectancy_age group 1 (years)	73	73	73	Fixed	Central Statistics Office[309]
Life expectancy_age group 2 (years)	48	48	48	Fixed	
Life expectancy_age group 3 (years)	27	27	27	Fixed	
Life expectancy_age group 4 (years)	18	18	18	Fixed	
Life expectancy_age group 5 (years)	14	14	14	Fixed	
Life expectancy_age group 6 (years)	8	8	8	Fixed	
All-cause mortality rate_age group 1	0.02%	0.02%	0.02%	Fixed	Central Statistics Office[287]
All-cause mortality rate_age group 2	0.08%	0.08%	0.08%	Fixed	
All-cause mortality rate_age group 3	0.44%	0.44%	0.44%	Fixed	
All-cause mortality rate_age group 4	1.13%	1.13%	1.13%	Fixed	
All-cause mortality rate_age group 5	1.93%	1.93%	1.93%	Fixed	
All-cause mortality rate_age group 6	7.01%	7.01%	7.01%	Fixed	

A6.5 Medication included for estimating the average cost of prescription medication for adults and children

Treatment options for influenza*	Description
Amoxicillin	Antibiotic - Adult
Doxyxycline	Antibiotic - Adult
Clarithromycin	Antibiotic - Adult
Amoxicillin 250mg/5ml	Antibiotic - Child
Clarithromycin 250mg/5ml	Antibiotic - Child
Exputex®	Expectorant (cough bottle)
Paracetamol	Analgesic / anti-pyretic - Adult
Ibuprofen	Analgesic / anti-pyretic - Child
Mometasone nasal spray	Nasal spray (steroid)
Oseltamavir (Tamiflu®)	Antiviral / neuraminidase inhibitor
Tamiflu Powder for Oral Suspension®	Antiviral / neuraminidase inhibitor
Prednisolone (Deltacortril®)	Oral Steroid - Adult
Prednisolone (Prednesol®)	Oral Steroid - Child

*The average cost of prescription medication (per person) was estimated based on the composition of a prescription being antibiotic (41%), analgesic (31%) and 'other' (28%).

A6.6 Medication included for estimating the average cost of over-the-counter medication for adults and children

Treatment options for influenza*	Description
Adult	
Paracetamol	Analgesia/Antipyretic - Adult
Ibuprofen	Analgesia/Antipyretic - Adult
Psuedoephedrine tablets	Decongestant
Psuedoephedrine nasal spray	Decongestant
Exputex®	Expectorant (cough bottle)
Bronchostop®	Anti-tussive (cough bottle)
Difflam® throat spray	Anti-sore throat
Strepsils plus®	Anti-sore throat
Child	
Calpol® (under 6 years)	Analgesia/Antipyretic - Child
Calpol® (6+ years)	Analgesia/Antipyretic - Child
Nurofen® (under 6 years)	Analgesia/Antipyretic - Child
Nurofen® (6+ years)	Analgesia/Antipyretic - Child
Exputex®	Expectorant (cough bottle)
Bronchostop Junior®	Anti-tussive (cough bottle)

A6.7 Scenario analysis results for largest net monetary benefit of all three vaccination strategies at a willingness-to-pay threshold of €45,000 per QALY, by unit cost of vaccine

Vaccination strategy with the largest net monetary benefit at a willingess-to-pay threshold of €45,000 per QALY									
		High-dose IIV							
Standard IIV	Adjuvanted IIV	€15.00	€20.00	€25.00	€30.00	€35.00	€36.27	€40.00	€45.00
€5.00	€10.99	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€5.00	€12.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€5.00	€14.00	High-dose	High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€16.00		High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€16.49		High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€18.00		High-dose	High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€20.00			High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€22.00			High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€24.00			High-dose	Standard	Standard	Standard	Standard	Standard
€5.00	€25.00				Standard	Standard	Standard	Standard	Standard
€7.50	€10.99	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€12.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€14.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€16.00		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€16.49		High-dose	High-dose	High-dose	Standard	Standard	Standard	Standard
€7.50	€18.00		High-dose	High-dose	High-dose	Standard	Standard	Standard	Standard
€7.50	€20.00			High-dose	High-dose	Standard	Standard	Standard	Standard
€7.50	€22.00			High-dose	High-dose	Standard	Standard	Standard	Standard
€7.50	€24.00			High-dose	High-dose	Standard	Standard	Standard	Standard
€7.50	€25.00				High-dose	Standard	Standard	Standard	Standard
€10.00	€10.99	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€12.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€14.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€16.00		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€16.49		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€18.00		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€20.00			High-dose	High-dose	Standard	Standard	Standard	Standard
€10.00	€22.00			High-dose	High-dose	Standard	Standard	Standard	Standard
€10.00	€24.00			High-dose	High-dose	Standard	Standard	Standard	Standard
€10.00	€25.00				High-dose	Standard	Standard	Standard	Standard
€10.99	€12.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€14.00	High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€16.00		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€16.49		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€18.00		High-dose	High-dose	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€20.00			High-dose	High-dose	High-dose	Standard	Standard	Standard
€10.99	€22.00			High-dose	High-dose	High-dose	Standard	Standard	Standard
€10.99	€24.00			High-dose	High-dose	High-dose	Standard	Standard	Standard
€10.99	€25.00				High-dose	High-dose	Standard	Standard	Standard

Key: IIV – inactivated influenza vaccine.

Indicates results of base-case scenario.

A6.8 Scenario analysis results for incremental budget impact of all three vaccination strategies, by unit cost of vaccine

Vaccination strategy with the lowest one-year incremetal budget impact									
Standard IIV	**Adjuvanted IIV**	€15.00	€20.00	€25.00	€30.00	€35.00	€36.27	€40.00	€45.00
€5.00	€10.99	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€5.00	€12.00	High-dose	Standard	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€14.00	High-dose	Standard	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€16.00		Standard	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€16.49		Standard	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€18.00		Standard	Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€20.00			Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€22.00			Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€24.00			Standard	Standard	Standard	Standard	Standard	Standard
€5.00	€25.00				Standard	Standard	Standard	Standard	Standard
€7.50	€10.99	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€12.00	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€7.50	€14.00	High-dose	Standard	Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€16.00		Standard	Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€16.49		Standard	Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€18.00		Standard	Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€20.00			Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€22.00			Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€24.00			Standard	Standard	Standard	Standard	Standard	Standard
€7.50	€25.00				Standard	Standard	Standard	Standard	Standard
€10.00	€10.99	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€12.00	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€14.00	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€16.00		High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.00	€16.49		High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€10.00	€18.00		High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€10.00	€20.00			Standard	Standard	Standard	Standard	Standard	Standard
€10.00	€22.00			Standard	Standard	Standard	Standard	Standard	Standard
€10.00	€24.00			Standard	Standard	Standard	Standard	Standard	Standard
€10.00	€25.00				Standard	Standard	Standard	Standard	Standard
€10.99	€12.00	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€14.00	High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€16.00		High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€16.49		High-dose	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted	Adjuvanted
€10.99	€18.00		High-dose	Standard	Standard	Standard	Standard	Standard	Standard
€10.99	€20.00			Standard	Standard	Standard	Standard	Standard	Standard
€10.99	€22.00			Standard	Standard	Standard	Standard	Standard	Standard
€10.99	€24.00			Standard	Standard	Standard	Standard	Standard	Standard
€10.99	€25.00				Standard	Standard	Standard	Standard	Standard

Key: IIV – inactivated influenza vaccine.

Indicates results of base-case scenario.

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