Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Rapid health technology assessment of the extension of the seasonal influenza vaccination programme to include those aged 50 to 64 years (general population)

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Safer Better Care

About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority 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.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. 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 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 health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these 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 services, in conjunction 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 or 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, anyone can pay for an annual influenza vaccine, but several population groups (for example, those aged 65 years or older, healthcare workers, those with certain medical conditions, pregnant women, and carers) are eligible to receive a free annual influenza vaccine through the Health Service Executive's Seasonal Influenza Vaccination Programme.

As a temporary measure for the 2021-2022 season, reimbursement of vaccination for those aged 50 to 64 years (and not already eligible for a free influenza vaccine) was authorised by the Minister for Health, to minimise the overall burden associated with viral respiratory infections given the widespread circulation of SARS-CoV-2 at that time. The purpose of this rapid health technology assessment (HTA) was to inform a decision as to whether this group should again be included as a temporary measure for the 2023-2024 season.

Work on the rapid 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 rapid 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 CEO & Director of Health Technology Assessment

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Expert Advisory Group membership

The membership of the Expert Advisory Group was as follows:

Dr Geraldine Casey	Specialist in Public Health Medicine, Health Protection Surveillance Centre
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HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this rapid health technology assessment. Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed above who provided advice and information. We would also like to express our gratitude to the Health Protection Surveillance Centre, Healthcare Pricing Office of the Health Service Executive (HSE) and the Primary Care Reimbursement Service of the HSE, for sharing and advising on the data used.

Conflicts of Interest

Dr Hanlon is a general practitioner who derives a small portion of his 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 Department of Health

At the request of the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a rapid health technology assessment (HTA) on expanding the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme in Ireland (for the 2023-2024 season) to include reimbursement of standard quadrivalent influenza vaccines (QIVs) for those aged 50 to 64 years in the general population (that is, those not at increased risk of severe disease). Given the short timeline within which the information was required, reviews of clinical effectiveness and safety were not undertaken as this evidence base has been established in principle. Where possible, data were disaggregated into five-year subgroups: 50 to 54 years, 55 to 59 years and 60 to 64 years.

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

- Annual vaccination is an important preventative measure to reduce the burden associated with seasonal influenza.
- Available vaccines include standard trivalent influenza vaccines (TIVs) and QIVs, as well as new and enhanced vaccines developed to improve vaccine effectiveness. Influenza vaccines may be co-administered with a COVID-19 vaccine. In Ireland, as of May 2023, there are two standard QIVs licensed and marketed for seasonal influenza.
- 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. However, in the context of the COVID-19 pandemic, some countries opted to vaccinate specific age groups regardless of their risk status to reduce overall burden on the healthcare system.
- An overview of national-level influenza vaccination recommendations in the EU/EEA and UK for those aged 50 years and older identified differences in vaccine policy. Considering specifically those in the general population (that is, not at increased risk of severe disease) aged 50 to 64 years:
    - Seven EU/EEA countries reimburse influenza vaccination for part of the target population within their national immunisation programme.
    - Five (Germany, Greece, Hungary, Iceland and Netherlands) of the seven EU/EEA countries limit reimbursement to those aged 60 years and older;

Slovakia reimburses vaccination from age 59 years and Malta from age 55 years.

- Six (Greece, Hungary, Iceland, Malta, Netherlands and Slovakia) of the seven EU/EEA countries reimburse standard TIVs or QIVs; Germany reimburses high-dose QIVs.
- In the UK, influenza vaccination was reimbursed for those aged 50 to 64 years in the general population (that is, not at increased risk of severe disease) for the 2020-2021, 2021-2022 and 2022-2023 influenza seasons.
- England reimbursed standard QIVs, but newer and enhanced QIVs were available. In the rest of the UK, newer and enhanced QIVs were recommended and reimbursed.
- On 25 May 2023, the UK government reversed this decision due to uncertainty surrounding the cost-effectiveness of this intervention. As such, those aged 50 to 64 years and not at increased risk of severe disease are no longer eligible for a free influenza vaccination.

- Incidence data were sourced from the Health Protection Surveillance Centre (HPSC) in Ireland. Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), there has been substantial variability from seasons 2010-2011 to 2022-2023 in terms of the annual number of notified influenza cases (mean=738, range: 61 to 2,078).
  - For the most recent season (2022-2023), the notified influenza case rate per 100,000 in the total population in Ireland aged 50 to 64 years was 256.9 (n=2,078). It is acknowledged that this is an underestimate of the total burden as a proportion of those with influenza will not undergo testing to be formally identified as a case.
  - Again, excluding the seasons influenced by COVID-19, from seasons 2010-2011 to 2022-2023, there was substantial variability in the number of laboratory-confirmed influenza-related hospital admissions (mean=254, range: 13 to 608), hospital admissions with an ICU stay (mean=26, range: 2 to 49) and mortality (mean=12, range: 0 to 29) in those aged 50 to 64 years.
  - For the most recent season (2022-2023), the laboratory-confirmed influenza-related hospital admission rate was 67.3 (n=544), hospital admission with an ICU stay rate was 5.3 (n=43) and mortality rate was 2.1 (n=17).

- Across all the seasons included in the analysis (2020-2011 to 2022-2023), the burden of disease was typically highest in those aged 60 to 64 years.

- While there are differences in the rates of influenza cases and outcomes across the three age bands, it is unclear whether the differences observed would result in substantial benefits for one subgroup over another. Across all the seasons included in this analysis, the average number of laboratory-confirmed:

  - influenza cases per annum was 231 (range: 19 to 684) in those aged 50 to 54 years, 242 (range: 20 to 629) in those aged 55 to 59 years, and 266 (range: 22 to 765) in those aged 60 to 64 years.

  - influenza-related hospital admissions per annum was 69 (range: 0 to 164) in those aged 50 to 54 years, 81 (range: 8 to 207) in those aged 55 to 59 years, and 105 (range: 5 to 238) in those aged 60 to 64 years.

  - influenza-related hospital admissions which included an ICU stay per annum was 7 (range: 0 to 19) in those aged 50 to 54 years, 8 (range: 0 to 19) in those aged 55 to 59 years, and 10 (range: 1 to 21) in those aged 60 to 64 years.

  - influenza-related deaths per annum was 3 (range: 0 to 7) in those aged 50 to 54 years, 4 (range: 0 to 13) in those aged 55 to 59 years, and 6 (range: 0 to 13) in those aged 60 to 64 years.

- Hospital Inpatient Enquiry System (HIPE) data (which reflect the public acute hospital setting) showed substantial variability over time in relation to the number of discharges, length of stay (LOS) and total bed days over time. For those aged 50 to 64 years, data showed that between 2010 and 2022 (excluding 2020 and 2021 which are not representative due to the COVID-19 pandemic) there were, on average:

  - 199 (range: 17 to 571) discharges with a primary diagnosis of influenza per annum. The mean LOS was 6 days and the mean total bed days was 1,244 days per annum.

  - 19 (range: 7 to 40) discharges with a primary diagnosis of influenza that included an ICU stay per annum. The mean LOS was 14 days and the mean total bed days associated with these discharges was 314 days per annum.

  - 112 (range: 10 to 293) discharges with a secondary diagnosis of influenza per annum. 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 burden associated with influenza.

- A costing analysis was conducted to estimate the potential costs and benefits associated with expanding the HSE's Seasonal Influenza Vaccination Programme to include those aged 50 to 64 years in the general population for the 2023-2024 influenza season. The potential impact on health outcomes and healthcare utilisation of extending vaccination is subject to considerable uncertainty. Aside from the coverage, key parameters include the vaccine effectiveness, likelihood of hospitalisation and ICU admission, and typical length of stay in hospital and ICU. A wide range of projected influenza vaccine uptake rates were assessed to ascertain the potential costs and effects of extending vaccination eligibility.
- Based on figures from the Central Statistics Office, the total population aged 50 to 64 years is estimated to be 914,379.
- HPSC data report that the influenza vaccination uptake rate over the past two influenza seasons was approximately 28% in those aged 50 to 64 years. These uptake data reflect vaccination reimbursed through the HSE's Seasonal Influenza Vaccination Programme expressed as a percentage of the total population.The data underestimate total influenza vaccine uptake as they exclude instances where individuals or employers (as part of an occupational health scheme) pay for the vaccine privately.
- If vaccine uptake for this cohort increases from 28% (recent uptake) to 35% (which is considered achievable, supported by an appropriate public health information campaign), the mean incremental cost to the HSE of extending eligibility for the 2023-2024 season is estimated at approximately €2.27 million. This comprises €1.52 million in fees for administering the vaccine and €0.75 million for the vaccine (assuming a vaccine cost of €10 plus 23% VAT per dose).
    - Given the uncertainty in vaccine cost, a range of costs were modelled from a low of €5 to a high of €15 per dose. Based on this, mean incremental vaccine costs could range from €0.38 million (€5 plus 23% VAT per dose) to €1.13 million (€15 plus 23% VAT per dose).
- Given that there appears to be a trend of increasing rates of influenza, and influenza-related hospital discharges, hospital discharges with an ICU visit and mortality with increased age, a decision could be made to limit the programme extension to one or more of the five-year age band subgroups within this cohort.
    - Under the same assumptions of an uptake increase to 35% and using a vaccine cost of €10 (plus 23% VAT per dose), the estimated total mean

incremental cost is approximately €0.68 million if extended just to those aged 60 years and older and €1.43 million if extended just to those aged 55 years and older.

- If vaccine uptake increases from 28% to 35%, it is estimated that a mean of 77 influenza cases, 22 influenza-related hospital discharges and 136 influenza-related bed days could be avoided. The corresponding mean reduction in influenza-related hospital costs for a 35% influenza vaccination uptake rate is estimated at €0.11 million.

- There is considerable uncertainty surrounding the potential increase in uptake that could be achieved and surrounding the potential benefits of extending eligibility. In the absence of disaggregated data, the analysis assumed equal benefit for all vaccine recipients in this age range. However, those at increased risk of severe disease are already eligible for a free influenza vaccination. As vaccination uptake rates increase, the risk profile of the population may change, so that the additional benefits are not proportional.

- In the context of the current HSE Seasonal Influenza Vaccination Programme which provides access to free influenza vaccination to healthcare workers and those identified as being at increased risk of severe disease, there is a relatively modest absolute number of influenza-related hospitalisations each year in this age group. Given this, and the substantial year-on-year variability in vaccine effectiveness, the potential for a reduction in demand for hospital care associated with an expansion of the programme is likely to be small.

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

- Influenza is a seasonal contagious respiratory illness. While symptoms may be mild, some subgroups are at increased risk of serious complications. The burden of disease varies from one year to another, depending on circulating strains and population immunity.

- Over the last two influenza seasons, vaccine uptake has averaged 28% in those aged 50 to 64 years. Based on the impact of extending eligibility in the 2020-2021 season, the absolute increase in uptake may be modest unless supported by a public health information campaign.

- The incremental cost of extending the HSE Seasonal Influenza Vaccination Programme for the 2023-2024 influenza season to include those aged 50 to 64

years (in the general population) is estimated at €2.3 million assuming total uptake in this age group increases from 28% to 35%.

- There is substantial uncertainty in relation to the potential costs and benefits associated with expanding reimbursement to this population group. In the context of the existing vaccination programme which provides access to free influenza vaccination to those identified as being at increased risk of exposure or of severe disease, there is a relatively modest absolute number of influenza-related hospitalisations in this age group. Given this, and the substantial year-on-year variability in vaccine effectiveness, the potential for a reduction in demand for hospital care is likely to be small.
- Given an apparent trend of increasing burden with increased age, a decision could be made to limit the programme extension. Under the same uptake and cost assumptions, the estimated incremental cost for 2023-2024 is €0.68 million if extended just to those aged 60 years and older and €1.43 million if extended to those aged 55 years and older.
- In the event of a decision to expand the HSE Seasonal Influenza Vaccination Programme, consideration should be given to:
    - Enhanced data collection (for example, regarding the risk status of those availing of vaccination and the vaccination status of influenza cases) to inform changes to the Programme.
    - Public health information campaigns for those involved in administering the vaccine, and to empower individuals and support informed decision-making.

Executive Summary

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The aim of this rapid HTA was to inform a decision on expanding the influenza vaccination programme in Ireland to include reimbursement of standard quadrivalent influenza vaccines (QIVs) for those aged 50 to 64 years old in the general population (that is, those not included in one of the existing eligible groups). This rapid HTA considered the following domains:

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

Background

Following a request from the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a rapid HTA in relation to the inclusion of the 50 to 64 year age group in the general population (that is, those not included in one of the existing eligible groups) in the influenza vaccination programme in Ireland as a temporary measure for the 2023-2024 season.

Description of the technology and international practice

The focus of this rapid HTA is seasonal influenza. 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 (for example, those aged 65 years and older and those with certain medical conditions) have an increased risk of severe disease and may require hospitalisation. Annual vaccination is an important preventative measure to reduce the burden associated with seasonal influenza. Available vaccines include standard trivalent (TIV) and quadrivalent (QIV) vaccines as well as new and enhanced vaccines developed to improve vaccine effectiveness. As of May 2023, Ireland two standard quadrivalent influenza vaccines (QIVs) licensed and marketed for seasonal influenza.

Influenza vaccination policies for the EU/EEA and UK were reviewed for the 2023-2024 influenza season. In total, seven EU/EEA countries reimburse influenza vaccination for part of the target population as part of their national immunisation

programme. Five (Germany, Greece, Hungary, Iceland and Netherlands) of the seven EU/EEA countries limit reimbursement to those aged 60 years and older; Slovakia reimburses vaccination from age 59 years and Malta from age 55 years. Six (Greece, Hungary, Iceland, Malta, Netherlands and Slovakia) of the seven EU/EEA countries reimburse standard TID or QIV vaccines; Germany reimburses high dose QIVs. In the UK, for previous influenza seasons, vaccination of those aged 50 to 64 years and not at increased risk of severe disease was recommended and reimbursed. In May 2023, the UK government reversed this decision due to uncertainty surrounding the cost effectiveness of the intervention. As such, those aged 50 to 64 years and not at increased risk of severe disease are no longer eligible for a free influenza vaccination.

Epidemiology and burden of disease

Influenza is a contagious respiratory illness and immunity provided by vaccines is temporary, making a large proportion of the population susceptible to infection each season. Data on the epidemiology and burden of influenza were sourced from the Health Protection Surveillance Centre (HPSC) and the Hospital Inpatient Enquiry System (HIPE) in Ireland. Data were not disaggregated by risk status, therefore the data presented reflect the burden of disease for the total population (that is, including those at increased risk of severe disease) aged 50 to 64 years. Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), there has been substantial variability from seasons 2010-2011 to 2022-2023 in terms of the annual number of notified cases (mean=738, range: 61 to 2,078). For the most recent season (2022-2023), the notified influenza case rate per 100,000 in the total population in Ireland aged 50 to 64 years was 256.9 (n=2,078). It is acknowledged that this is an underestimate of the total burden as a proportion of those with influenza will not undergo testing to be formally identified as a case.

Again, excluding the seasons influenced by COVID-19, from seasons 2010-2011 to 2022-2023, there was substantial variability in and the number of laboratory-confirmed influenza-related hospital admissions (mean= 254, range: 13 to 608), hospital admissions with an intensive care unit (ICU) stay (mean=26, range: 2 to 49) and mortality (mean=12, range: 0 to 29) in those aged 50 to 64 years.

For the 2022-2023 influenza season, in those aged 50 to 64 years the following laboratory-confirmed rates per 100,000 population were reported:

- influenza-related hospital admission rate of 67.3 (n=544)
- influenza-related hospital admission with an ICU stay rate of 5.3 (n=43)
- influenza-related mortality rate of 2.1 (n=17).

Across all the seasons included in the analysis (2020-2011 to 2022-2023), the burden of disease was typically highest in those aged 60 to 64 years. While there were differences in the rates of influenza cases and outcomes across the three age bands, it is unclear whether the differences observed would result in substantial benefits for one subgroup over another.

In relation to the number of discharges, length of stay (LOS) and total bed days over time, between 2010 and 2022 (excluding 2020 and 2021 which are not representative due to COVID-19) the data for those aged 50 to 64 years show that, on average, there were:

- 199 (range: 17 to 571) discharges with a primary diagnosis of influenza per annum. The mean LOS was 6 days and the mean total bed days was 1,244 days per annum.
- 19 (range: 7 to 40) discharges with a primary diagnosis of influenza that included an ICU stay per annum. The mean LOS associated with these discharges was 14 days and the mean total bed days was 314 days per annum.
- 112 (range: 10 to 293) discharges with a secondary diagnosis of influenza per annum. 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 burden associated with influenza.

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.

Costing analysis

A costing analysis was conducted to estimate the potential costs and benefits associated with extending the HSE's Seasonal Influenza Vaccination Programme for the 2023-2024 season, to include those aged 50 to 64 years in the general population. In the absence of national data by risk category, potential costs and benefits were calculated for the total population aged 50 to 64 years regardless of their risk status.

Based on figures from the Central Statistics Office figures, the total population aged 50 to 64 years is estimated to be 914,379. HPSC data report that the influenza vaccination uptake rate over the past two influenza seasons was approximately 28% in this age group. This figure is an underestimate, for example, it does not include those receiving an influenza vaccination at work as part of an employer occupational

health scheme. However, it is unlikely that extending eligibility to the target population will result in changes to employer practice around providing vaccination to employees. As such, it should not affect the incremental budget impact for the HSE as most employees within the target group will continue to avail of it through their employer.

If vaccine uptake for this cohort increases from 28% (recent uptake) to 35% (which is considered achievable, supported by an appropriate public health information campaign), the mean incremental cost of extending eligibility for the 2023-2024 season is estimated at approximately €2.27 million. This comprises €1.52 million in fees for administering the vaccine and €0.75 million for the vaccine (assuming a vaccine cost of €10 plus 23% VAT per dose). Given the uncertainty in vaccine cost, a range of costs were modelled from a low of €5 to a high of €15 per dose. Based on this, vaccine costs could range from €0.38 million (€5 plus 23% VAT per dose) to €1.13 million (€15 plus 23% VAT per dose).

Given that there appears to be a trend of increasing rates of influenza, and influenza-related hospital discharges, hospital discharges with an ICU stay and mortality with increased age, a decision could be made to limit the programme extension to one or more of the five-year age band subgroups within this cohort. Under the same assumptions of an uptake increase to 35% and using a vaccine cost of €10 (plus 23% VAT), the estimated total mean incremental cost is approximately €0.68 million if extended just to those aged 60 years and older and €1.43 million if extended just to those aged 55 years and older.

If a 35% influenza vaccination uptake rate was achieved, by extending eligibility to the target group and supported by a public health information campaign, relative to the current uptake rate of 28%, it is estimated that a mean of 77 influenza cases, 22 influenza-related hospital discharges and 136 influenza-related bed days would be avoided. The corresponding mean reduction in influenza related hospital costs would be €0.11 million.

There is considerable uncertainty surrounding the potential benefits of extending eligibility. The analysis assumed equal benefit for all vaccine recipients when in reality, those at increased risk of severe disease are already eligible for a free influenza vaccination. Additionally, based on historic uptake rates, a 35% vaccination coverage rate may not be achieved.

Conclusions

Annual seasonal vaccination can be effective in reducing the incidence of influenza, including the incidence of severe disease. However, there is substantial uncertainty in relation to the potential costs and benefits associated with expanding

reimbursement of vaccination to those aged 50 to 64 years in the general population (that is, those not included in one of the existing eligible groups). The estimated mean incremental cost to the HSE of expanding reimbursement for the 2023 to 2024 influenza season is approximately €2.3 million if uptake in those aged 50 to 64 years increases from 28% to 35%. However, as vaccination uptake increases, the risk profile of the vaccinated population may change, so that the additional benefits achieved are not proportional. In the context of the existing HSE Seasonal Influenza Vaccination Programme which provides access to free influenza vaccination to those at identified as being at increased risk of exposure or of severe disease there is a relatively modest absolute number of influenza-related hospitalisations in this age group. Given this, and the substantial year-on-year variability in vaccine effectiveness, the potential for a reduction in demand for hospital care is likely to be small.

Plain language summary

Flu (influenza) is an acute viral infection that infects the lungs and upper airways. While some people recover quickly, others develop severe complications requiring hospitalisation. The flu virus spreads every winter. The annual flu vaccine is the best way to protect against the flu. In general, people who get the vaccine will be protected from the flu. Those who still get the flu after vaccination should have milder symptoms and recover faster. As the protection fades over time, people need to get the flu vaccine every year. As flu strains change, the content of the vaccine is updated each year to match the circulating strain.

In Ireland, a free annual flu vaccination is provided by the Health Service Executive (HSE) to certain risk groups (such as healthcare workers) 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 and people of any age with certain medical conditions.

The Department of Health asked the Health Information and Quality Authority (HIQA) to look at the impact of making flu vaccination free for everyone aged 50 to 64 years. This assessment looked at the benefits and costs to the HSE if the flu vaccination programme was extended as a temporary measure for the 2023-2024 flu season.

We looked to see what other European countries recommend for this age group. No European country provides the flu vaccine free of charge to everyone aged between 50 and 64 years. Five countries provide it free of charge to all those aged 60 years and older. One country provides it to everyone aged 59 years and older. One country provides it to all those aged 55 years and older. The UK government provided a free flu vaccine to everyone aged 50 to 64 years for a number of years. This will not to continue for the 2023-2024 flu season.

The number of people diagnosed with the flu and the number who require hospitalisation varies a lot from year to year. For the most recent season (2022-2023), over 2,000 people in Ireland aged between 50 and 64 years had a confirmed flu diagnosis. Of these, over 500 were admitted to hospital, over 40 needed to be admitted to ICU for some of their hospital stay, and 17 people died. These numbers may include people who were at increased risk of severe disease.

In Ireland, there are approximately 900,000 people aged between 50 and 64 years. If uptake increased, so that about one third of this age group got a free flu vaccine, this would cost the HSE an additional €2.3 million in 2023-2024.

Vaccination can be very effective in preventing flu and severe illness due to flu. However, there is a lot of uncertainty about the potential costs and benefits with extending the current vaccination programme. The potential benefits for the HSE in extending the flu vaccination programme for the 2023-2024 season may be quite small.

List of abbreviations used in this report

ACSC	Ambulatory care sensitive condition
ARI	Acute respiratory infection
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIDR	Irish Computerized Infectious Disease Reporting System
CSO	Central Statistics Office
EAG	Expert Advisory Group
ECDC	European Centre for Disease Control
EEA	European Economic Area
EU	European Union
GP	General practitioner
HA	Hemagglutinin
HIPE	Hospital Inpatient Enquiry System
HIQA	Health Information And Quality Authority
HPRA	Health Products Regulatory Authority
HPSC	Health Protection And Surveillance Centre
HSE	Health Service Executive
HTA	Health Technology Assessment
ICD	International classification of disease
ICGP	Irish College of General Practitioners
ICU	Intensive care unit
IIVs	Inactivated influenza vaccine
ILI	Influenza like illness
JCVI	Joint Committee on Vaccination and Immunisation

LAIVs	Live attenuated influenza vaccine
LOS	Length of stay
NA	Neuraminidase
NHS	National Health Service
NIAC	National Immunization Advisory Committee
OR	Odds ratio
PPV23	23-valent pneumococcal polysaccharide vaccine
QIV	Quadrivalent influenza vaccine
aQIV	Adjuvanted quadrivalent influenza vaccine
cQIV	Cell-based quadrivalent influenza vaccine
HD-QIV	High dose quadrivalent influenza vaccine
rQIV	Recombinant HA quadrivalent influenza vaccine
RNA	Ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TIV	Trivalent influenza vaccine
WHO	World Health Organization

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.[1] Annual influenza vaccination facilitates prevention of seasonal influenza as well as the prevention of onward transmission of the illness to others. Other preventative measures to compliment 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] In Ireland, guidance from the National Immunisation Advisory Committee (NIAC) in Ireland recommends vaccination using a quadrivalent vaccine (QIV) for those aged 50 to 64 years.[4] However, while vaccination for selected individuals in this age group may be reimbursed as part of the influenza vaccination programme in Ireland (for example, those who are healthcare workers or who are at increased risk of severe influenza), this age group is not routinely included as an at-risk group for whom vaccination is reimbursed.[5]

As a temporary measure for the 2021-2022 season, reimbursement of vaccination for this age group was authorised by the Minister for Health, to minimise the overall burden associated with viral respiratory infections, given the widespread circulation of SARS-CoV-2 in the community at that time.[6] In order to inform a decision as to whether vaccination for this group should be reimbursed again as a temporary measure for the 2023-2024 season, the Department of Health requested that HIQA complete a rapid health technology assessment (HTA) on expanding the seasonal influenza vaccination programme in Ireland to include reimbursement of standard QIVs for those aged 50 to 64 years old in the general population. Given the short timeline in which the information is required, reviews of clinical effectiveness and safety were not undertaken as this evidence base has been established in principle. Similarly, given that this will inform an interim decision rather than a permanent change to the programme, a review of the cost-effectiveness literature was not undertaken. Where possible, data were disaggregated into five-year subgroups: 50 to 54 years, 55 to 59 years and 60 to 64 years.

1.2 Terms of reference

Following the request from the Department of Health a set of objectives were developed with consideration to the evidence needs of the decision maker.

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

- Describe the standard QIVs available on the Irish market.
- Summarise international influenza vaccination programmes for those aged 50 to 64 years old.
- Describe the epidemiology and burden of disease associated with influenza in those aged 50 to 64 years (general population) in Ireland.
- Describe the uptake of influenza vaccination in those aged 50 to 64 years (general population) in Ireland.
- Provide an indication of the likely additional costs associated with the expansion of the influenza vaccination programme in Ireland.
- Based on the evidence in this assessment, provide advice to the Department of Health on expanding the influenza vaccination programme in Ireland to include reimbursement of vaccination for those aged 50 to 64 years old.

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 decision makers, clinical experts, public health experts and methodological expertise. The role of the EAG was to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the EAG is available in the acknowledgements 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 rapid HTA by participating in an evaluation of the process upon the conclusion of the assessment.

A draft of the rapid HTA was prepared by the evaluation team and disseminated to the EAG for review prior to their meeting. At the meeting, the terms of reference for the HTA were reviewed and the draft evidence discussed. Following incorporation of feedback, a revised draft of the report was recirculated to the EAG for review and feedback. The draft report was approved by the Executive Management Team in HIQA in July 2023. The final report was submitted to the Department of Health as advice and published on the HIQA website.

2 Description of the technology and international practice

Key points

- Annual vaccination is an important preventative measure to reduce the burden associated with seasonal influenza.
- Available vaccines include standard trivalent influenza vaccines (TIVs) and QIVs as well as new and enhanced vaccines developed to improve vaccine effectiveness. Influenza vaccines may be co-administered with a COVID-19 vaccine. In Ireland, as of May 2023, there are two standard QIVs licensed and marketed for seasonal influenza.
- 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. However, in the context of the COVID-19 pandemic, some countries opted to vaccinate specific age groups regardless of their risk status to reduce overall burden on the healthcare system.
- An overview of national-level influenza vaccination recommendations in the EU/EEA and UK for those aged 50 years and older identified differences in vaccine policy. Considering specifically those in the general population (that is, not at increased risk of severe disease) aged 50 to 64 years:
    - Seven EU/EEA countries reimburse influenza vaccination for part of the target population within their national immunisation programme.
    - Five (Germany, Greece, Hungary, Iceland and Netherlands) of the seven EU/EEA countries limit reimbursement to those aged 60 years and older; Slovakia reimburses vaccination from age 59 years and Malta from age 55 years.
    - Six (Greece, Hungary, Iceland, Malta, Netherlands and Slovakia) of the seven EU/EEA countries reimburse standard TIVs or QIVs; Germany reimburses high-dose QIVs.
    - In the UK, influenza vaccination was reimbursed for those aged 50 to 64 years in the general population (that is, not at increased risk of severe disease) for the 2020-2021, 2021-2022 and 2022-2023 influenza seasons.

- England reimbursed standard QIVs, but newer and enhanced QIVs were available. In the rest of the UK, newer and enhanced QIVs were recommended and reimbursed.
- On 25 May 2023, the UK government reversed this decision due to uncertainty surrounding the cost-effectiveness of this intervention. As such, those aged 50 to 64 years and not at increased risk of severe disease are no longer eligible for a free influenza vaccination.

2.1 Introduction

The purpose of this chapter is to describe the standard quadrivalent influenza vaccines (QIVs) licensed and marketed in Ireland that serve as the primary tool to prevent influenza A and B virus infection causing seasonal influenza. As detailed in the protocol, this chapter also provides background on the potential of influenza as a pathogen and the resulting disease. These issues will be explored in greater detail in Chapter 3. A description of the current influenza immunisation schedule in Ireland for those aged 50 to 64 years in the general population is provided. Lastly, a description of influenza immunisation programmes currently in place in the EU/EEA and UK is provided.

2.2 Pathogen

Influenza viruses are ribonucleic acid viruses from the Orthomyxoviridae family.[7] They circulate primarily through droplet transmission, aerosol transmission and contact transmission.[8] 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.[9] 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 (hemagglutinin (HA) and neuraminidase (NA)) present on the surface of the virus.[10] Influenza B viruses do not have sub-types but instead have two antigenically distinct lineages, Victoria and Yamagata.[9]

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.[8] Influenza has an incubation period of approximately two days (range 1-4 days). It

can be transmitted 24 hours before the onset of clinical symptoms and up to five days (or up to 7 days in children) after disease onset.[11]

2.3 Disease

The focus of this rapid assessment is seasonal influenza rather than pandemic influenza. Seasonal influenza 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, there have been four influenza pandemics within the last century (with an inter-pandemic interval range of 11 years to 39 years). These pandemics are the result of major changes in surface HA and NA glycoproteins which generate a new influenza A virus and subtype.[12]

Influenza A and influenza 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.[10] 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.[13] Seasonal influenza places a 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 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, 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 varies 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.[14] 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 or older.[5]

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.[13]

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).[13]

Additionally, patients infected with influenza can experience co-infection with other pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 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, co-morbidity and coinfection 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.[15]

2.4 Detection of influenza virus and immune response after infection

Diagnosis of influenza is primarily based on the presence of symptoms when the virus is known to be circulating. This often occurs in the primary care setting. However, there are several diagnostic tests that can be used to detect influenza viruses; these include rapid antigen tests, molecular assays and virus cultures.[13] Testing for respiratory viruses, including influenza, is recommended in certain circumstances (for example, in nursing home residents to identify outbreaks)[16] or as part of a differential diagnosis and to inform treatment decisions, for example in patients with complicated influenza or at risk of severe disease.

Following infection with influenza, innate and adaptive immune responses work to clear the infection.[17] This natural response to infection is relatively broad and long-lived.[18] However, due to antigenic drift (that is, evolution of influenza viruses which enable them to evade human humoral immunity), immunity following infection is not life-long.[17] Similarly, antigenic drift means the specific viral subtyping of the content of seasonal influenza vaccines changes annually. Subsequently, the induced immune response following immunisation is narrow and short-lived.[18]

2.5 Vaccines

This section is limited to standard QIVs currently licensed and marketed in Ireland for the population under review.

2.5.1 Vaccine description

In the mid-1930s, the first clinical trials of an inactivated influenza vaccine (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.[19] 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. Inactivated trivalent (TIV) and quadrivalent (QIV) influenza vaccines are now widely used.[20]

Influenza vaccines are most effective when they are strain-specific. These are vaccines that 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.[21] This network consists of a number of collaborative centres around the world that 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.[22]

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 (aged 65 years or older) or those taking immunosuppressants.[23] As such, new and enhanced influenza vaccines have been developed in an attempt to increase vaccine effectiveness. These include:

- adjuvanted QIVs (aQIV) – QIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response
- cell-based QIVs (cQIV) - QIVs manufactured using mammalian cell-culture
- recombinant HA QIVs (rQIV) – QIV manufactured using recombinant HA proteins instead of egg-derived processes
- high-dose QIVs (HD-QIV) - QIV which contain a fourfold increase of HA per strain, (that is, 60µg) instead of 15µg of HA typically included in standard dose QIVs.[24]

In Ireland, standard (egg-based) QIVs are recommended for the target population (those aged 50 to 64 years in the general population). As of May 2023, two standard

QIV seasonal influenza vaccines are licensed and marketed in Ireland.[25] The first (Quadrivalent Influenza Vaccine)[26] is manufactured by Sanofi Pasteur and was licensed in July 2016 and the second (Influvac tetra®)[27] is manufactured by Mylan IRE Healthcare Limited and was licensed in August 2017. Both are licensed for administration to the target population, and both were reimbursed as part of the 2022-2023 HSE's Seasonal Influenza Vaccination Programme. A summary of key characteristics of the licensed and marketed standard QIVs available in Ireland is provided in Table 2.1.

2.5.2 Co-administration with other vaccines

Quadrivalent Influenza Vaccine[26] and Influvac Tetra®[27] can be given at the same time as other vaccines; however, the incidence of adverse events may be higher compared to when these vaccines are administered alone. Separate injection sites and separate syringes should be used in the case of concomitant administration.

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.[28] 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 National Immunisation Advisory Committee (NIAC), COVID-19, seasonal influenza and 23-valent pneumococcal polysaccharide PPV23 vaccines can be co-administered.[29]

2.5.3 Administration and manufacturers stipulated storage

The manufacturer's instructions for Quadrivalent Influenza Vaccine and Influvac tetra® state that they should be administered by intramuscular or deep subcutaneous injection.[26, 27] The preferred sites for intramuscular injection for adults is the deltoid muscle.

Both vaccines are marketed as pre-filled syringes which should be stored in a refrigerator at 2°C to 8°C. Both vaccines should be allowed to reach room temperature before use and should be shaken before administration.[26, 27]

2.5.4 Dosing schedule

Both vaccines, the dose for adults is 0.5ml administered as a single, annual dose. Based on clinical experience with TIVs, 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.[26, 27]

Table Error! No text of specified style in document.**.1 Summary of key characteristics of standard quadrivalent influenza vaccines licensed and marketed in Ireland**

Trade name	Quadrivalent Influenza Vaccine[26]	Influvac tetra®[27]
Manufacturer	Sanofi Pasteur	Mylan IRE Healthcare Limited
License issued	15 July 2016	25 August 2017
Formulation	Per 0.5ml dose, influenza virus (inactivated, split) of the following strains*: ▪ A/Victoria/2570/2019 (H1N1)pdm09 - like strain (A/Victoria/2570/2019, IVR-215) 15 mcg HA ▪ A/Darwin/9/2021 (H3N2) - like strain (A/Darwin/9/2021, IVR-228) 15 mcg HA ▪ B/Austria/1359417/2021 - like strain (B/Michigan/01/2021, wild type) 15 mcg HA ▪ B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type) 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/Victoria/2570/2019(H1N1)pdm09 - like strain (A/Victoria/2570/2019, IVR-215) 15 mcg HA ▪ A/Darwin/9/2021 (H3N2) - like strain (A/Darwin/9/2021, SAN-010) 15 mcg HA ▪ B/Austria/1359417/2021 - like strain (B/Austria/1359417/2021, BVR-26) 15 mcg HA ▪ B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type) 15 mcg HA. *Propagated in fertilised hens' eggs from healthy chicken flocks.
Therapeutic indications	Prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine 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. The use of Quadrivalent Influenza Vaccine (split virion, inactivated) 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.

Key: HA, haemagglutinin; mcg, micrograms.

Note: The formulation of these vaccines complied with the WHO recommendations (Northern Hemisphere) and EU recommendations (as endorsed by the EMA's human medicines committee) for the 2022-2023 influenza season.

2.6 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. Figure 2.1 provides an overview of national-level influenza vaccination recommendations in the EU/EEA and UK for those aged 50 years and older. The figure distinguishes between recommendations for specific subgroups (that is, those who are at increased risk of infection and or severe disease), and general recommendations (that is, those in the general population who may get vaccinated regardless of risk). With the exception of Lithuania and Sweden, all countries have a general recommendation for annual vaccination for those aged 65 years and older, although there are differences in the recommended vaccine type. Specifically, for those aged 50 to 64 years, 19 countries recommend vaccination; however, recommendations differed with respect to:

- whether this was a general recommendation for everyone regardless of the risk status, or if the recommendation is for specific at-risk groups only
- the age at which vaccination should commence (that is, ≥50, ≥55, ≥59 or ≥60 years)
- the choice of vaccine (any IIV, TID, QIV or enhanced QIV)
- whether or not the recommended vaccine is funded as part of a national immunisation programme.

Figure Error! No text of specified style in document.**.1 Overview of influenza vaccination programmes in the EU/EEA and UK for those aged 50 years and older**

	Age groups (years)						
Countries	**50**	**54**	**55**	**59**	**60**	**64**	**≥65**
Austria	QIV*						aQIV*⅄
Belgium	QIV						QIV
Bulgaria							IIV*
Croatia	QIV						QIV
Cyprus	TIV*						TIV
Czech Republic	QIV						QIV
Denmark							QIV
Estonia							QIV*
Finland							QIV
France							QIV
Germany					HD-QIV		
Greece	TIV				TIV		
Hungary					TIV		
Iceland					QIV		
Ireland	QIV						QIV
Italy	TIV						TIV
Latvia							TIV
Liechtenstein							TIV
Lithuania							TIV
Luxembourg							QIV
Malta	TIV		TIV				
Netherlands					QIV		
Norway	QIV						QIV
Poland			TIV*				
Portugal							TIV
Romania							TIV*
Slovakia					QIV		
Slovenia	QIV						QIV
Spain	QIV						QIV
Sweden	TIV^						
UK	QIV/enhanced QIV◇						

Key:

	General recommendation
	Recommendation for certain subgroups only
*	Vaccination not funded as part of national immunisation scheme
⅄	Funding varies for population group
^	Funding varies by region
◇	Vaccine recommended varies depending on the nation
aQIV	Adjuvanted quadrivalent influenza vaccine
IIV	Inactivated influenza vaccine, that is, TIV or QIV (not specified)
QIV	Quadrivalent influenza vaccine
TIV	Trivalent influenza vaccine

Adapted from: Vaccine Scheduler, European Centre for Disease Prevention and Control[30]

Note: As of 25 May 2023, the UK government advised that, for the 2023-2024 season influenza, vaccination would no longer be reimbursed for those aged 50 to 64 years in the general population.

2.6.1 Influenza vaccination schedule in Ireland

For the 2021-2022 season, those aged 50 to 64 years in the general population were eligible for a free influenza vaccination (from their primary care provider or their local pharmacy) as part of the HSE's Seasonal Influenza Vaccination Programme in Ireland. Guidance from NIAC recommended a QIV for this population group.[4] The reimbursement of vaccination for this age group was authorised by the Minister for Health as a temporary measure, to minimise the overall burden associated with viral respiratory infections given the wide circulation of COVID-19 in the community at that time. For the 2022-2023 season, individuals in this age group could still receive an annual influenza vaccination privately, however, it was not reimbursed as part of the HSE programme in Ireland unless they met other criteria (for example, healthcare worker or elevated risk of severe disease).[5] This assessment is intended to support a decision regarding reimbursement for this age group for the 2023-2024 season.

2.6.2 Influenza vaccination schedules in the EU/EEA and UK

Table 2.2 provides an overview of the countries in the EU/EEA and UK that currently reimburse (or reimbursed for the 2022-2023 season) annual seasonal influenza vaccinations for those within the target population (that is, those aged 50 to 64 years in the general population). These vaccinations are provided by primary care providers and or community pharmacies. The programmes are summarised below stratified according to the age from which vaccination is (or was) reimbursed.

Reimbursement starting at age 50 years

Since the late 1960s, influenza immunisation has been recommended (and reimbursed for certain population groups) in the UK. Initially the aim was to directly protect those at increased risk of severe disease. The Joint Committee on Vaccination and Immunisation (JCVI) regularly reviews the list of conditions that constitute a clinical risk group and where vaccination is indicated. Subsequently, it provides advice to the UK Government regarding decisions on reimbursement. In 2000, the influenza vaccination programme was extended to the total population aged 65 years and over in the UK, regardless of risk status.

In July 2020, during the COVID-19 pandemic, the JCVI advised on extending the influenza vaccination programme in the UK as a temporary measure for the 2020-2021 influenza season;[31] this measure was also implemented for the 2021-2022[32] and 2022-2023 seasons.[33] The extension of the influenza vaccination programme (that is, to reimburse influenza vaccinations for those aged 50 to 64 years in the general population) was reflected across all four nations (England, Northern Ireland, Scotland and Wales); the only difference being the type of vaccination being

recommended for this group. Vaccinations were administered through primary care providers and community pharmacies. For the 2022-2023 season, the following approaches were adopted:

- In England, a standard QIV was reimbursed for those aged 50 to 64 years in the general population. Enhanced QIVs (cQIV and rQIV) were also reimbursed and could be used in this population, as long as this did not divert stock from those at increased risk of severe disease and those aged 65 years and over.[33]
- In Northern Ireland, a cQIV was reimbursed for those aged 50 to 64 years regardless of risk status.[34] A standard QIV was also available, but in smaller volumes as it was intended for use in those aged between six months and two years.[35]
- In Scotland, those aged 50 to 64 years in the general population were eligible for a cQIV.[36]
- In Wales, the vaccines reimbursed for those aged 50 to 64 years, regardless of risk status, were a cQIV and a rQIV. If these vaccines were unavailable, a standard QIV was also available.[37]

On 25 May 2023, the UK government advised that, for the 2023-2024 influenza season, vaccination would no longer be reimbursed for those aged 50 to 64 years in the general population.[38]

Reimbursement starting at age 55 years

In Malta, influenza vaccination is reimbursed for all those aged 55 years and older in the general population with the vaccine provided through primary care providers.[39] This is consistent with the approach used before the COVID-19 pandemic.[40] According to the European Centre for Disease Prevention and Control (ECDC) Vaccine Scheduler, a TIV is reimbursed for those aged 55 years and older.[30]

Reimbursement starting at age 59 years

In Slovakia[41] individuals are eligible for a free influenza vaccination from their primary care provider if they are 59 years and older, even if they are not at increased risk of severe disease. This is consistent with the approach used before the COVID-19 pandemic.[40] It is recommended that those aged 59 years and older receive a standard QIV.

Reimbursement starting at age 60 years

In Germany,[42] Greece,[43] Hungary,[44, 45] Iceland[46, 47] and the Netherlands,[48, 49] individuals are eligible for a free influenza vaccination if they are 60 years and older, even if they are not at increased risk of severe disease. This is consistent with vaccine policy in place in these countries before the COVID-19 pandemic, [40] although noting that the age at which individuals became eligible was reduced from 65 years to 60 years in Hungary for the 2014-2015 influenza season onwards.[40, 50] Countries differ in the recommended vaccine. In Germany, it is recommended that those aged 60 to 64 years receive a HD-QIV; recommended alternatives are cQIV, rQIV and aQIV.[42] In Greece[43] and Hungary,[44, 45] the recommendation is for a TIV; a QIV is recommended in Iceland[46, 47] and the Netherlands.[48, 49]

Table Error! No text of specified style in document.**.2 Countries in the EU/EEA and UK that reimburse influenza vaccination in the general population aged 50 to 64 years through a national programme**

Country Influenza season	Age (years) from which vaccine is reimbursed	Recommended vaccine type for those aged 50 to 64 years	Setting for administration	
			Primary care provider	Community pharmacy
Germany[42] 2023-2024	60	HD-QIV	✓	✓
Greece[43] 2023-2024	60	TIV	✓	✓
Hungary[44, 45] 2023-2024	60	TIV	✓	
Iceland[46, 47] 2023-2024	60	QIV	✓	✓
Malta[39] 2023-2024	55	TIV	✓	
Netherlands[48, 49] 2023-2024	60	QIV	✓	
Slovakia[41] 2023-2024	59	QIV	✓	
England[31-33] 2022-2023	50	QIV cQIV and rQIV also available, but prioritised for those aged ≥65 years	✓	✓
Northern Ireland[34, 35] 2022-2023	50	cQIV QIV also available, but in smaller volumes.	✓	✓
Scotland[51] 2022-2023	50	cQIV	✓	✓
Wales[37] 2022-2023	50	cQIV or rQIV	✓	✓

Key: QIV, Quadrivalent influenza vaccine (standard); cQIV, Cell-based quadrivalent influenza vaccine; HD-QIV, High-dose quadrivalent influenza vaccine; rQIV, Recombinant quadrivalent influenza vaccine; TIV, Trivalent influenza vaccine.

Note: As of 25 May 2023, the UK government advised that, for the 2023-2024 season influenza, vaccination would no longer be reimbursed for those aged 50 to 64 years in the general population.

2.7 Discussion

Annual vaccination is an important preventative measure to reduce the burden associated with seasonal influenza. While elimination of influenza is not feasible, annual influenza vaccination programmes aim to reduce the burden on health systems internationally 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 influenza vaccines available including a number of new and enhanced vaccines that have been developed specifically to improve vaccine effectiveness in individuals who are at higher risk of a suboptimal immune response. The focus of this rapid HTA is standard QIVs for use in those aged 50 to 64 years in the general population. In Ireland, as of May 2023, there are two standard QIVs licensed and marketed for seasonal influenza. While licensed and marketed for use, they are currently not reimbursed as part of the publicly-funded healthcare system for the general population aged 50 to 64 years. This is consistent with the approach adopted in many EU/EEA countries and the UK; while almost all countries recommend and reimburse vaccination for those aged 65 years and older, there is substantial heterogeneity in terms of the approach taken for those in the general population aged between 50 and 64 years. A review of data published by the ECDC and websites of public health agencies found that seven EU/EEA countries[39, 41-49] recommend and reimburse vaccination for part of the target population. These countries differ in terms of the age at which reimbursement commences and the choice of vaccine. Five of the seven EU/EEA countries (Germany, Greece, Hungary, Iceland and Netherlands)[42-49] limit reimbursement to those aged 60 years and older, with Slovakia[41] reimbursing the vaccine from age 59 years and Malta[39] from age 55 years. With the exception of Germany, reimbursement is limited to standard TIVs and QIVs. Differences in reimbursement may reflect differences in the demographics and disease burden of influenza in the different countries. The burden of influenza in Ireland is explored in detail in Chapter 3. Of note, the UK[31-35, 37, 51] included those in the general population aged between 50 and 64 years in their influenza vaccination programme as a temporary measure for the 2020-2021, 2021-2022 and 2022-2023 influenza seasons. However, on 25 May 2023 they reversed this decision for the 2023-2024 influenza season.[38] While the JCVI acknowledged that there is clear clinical benefit in vaccinating this population, it noted that the cost effectiveness of this intervention is uncertain and that it could divert funding from more cost-effective interventions, such as extension of the childhood immunisation programme to include secondary schools.[52]

3 Epidemiology and burden of disease

Key points

- Influenza is a seasonal contagious respiratory illness. Although in many cases the symptoms of the disease are mild, complications can occur. All age groups are impacted during influenza seasons, although proportions vary from one year to another, depending on dominating viruses and population immunity.
- Incidence data were sourced from the Health Protection Surveillance Centre (HPSC) in Ireland. Excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), there has been substantial variability from seasons 2010-2011 to 2022-2023 in terms of the annual number of notified influenza cases (mean=738, range: 61 to 2,078).
    - For the most recent season (2022-2023), the notified influenza case rate per 100,000 in the total population in Ireland aged 50 to 64 years was 256.9 (n=2,078). It is acknowledged that this is an underestimate of the total burden as a proportion of those with influenza will not undergo testing to be formally identified as a case.
    - Again, excluding the seasons influenced by COVID-19, from seasons 2010-2011 to 2022-2023, there was substantial variability in the number of laboratory-confirmed influenza-related hospital admissions (mean=254, range: 13 to 608), hospital admissions with an ICU stay (mean=26, range: 2 to 49) and mortality (mean=12, range: 0 to 29) in those aged 50 to 64 years.
    - For the most recent season (2022-2023), the laboratory-confirmed influenza-related hospital admission rate was 67.3 (n=544), hospital admission with an ICU stay rate was 5.3 (n=43) and mortality rate was 2.1 (n=17).
    - Across all the seasons included in the analysis (2020-2011 to 2022-2023), the burden of disease was typically highest in those aged 60 to 64 years.
- While there are differences in the rates of influenza cases and outcomes across the three age bands, it is unclear whether the differences observed would result in substantial benefits for one subgroup over another. Across all the seasons included in this analysis, the average number of laboratory-confirmed:

- influenza cases per annum was 231 (range: 19 to 684) in those aged 50 to 54 years, 242 (range: 20 to 629) in those aged 55 to 59 years, and 266 (range: 22 to 765) in those aged 60 to 64 years.
- influenza-related hospital admissions per annum was 69 (range: 0 to 164) in those aged 50 to 54 years, 81 (range: 8 to 207) in those aged 55 to 59 years, and 105 (range: 5 to 238) in those aged 60 to 64 years.
- influenza-related hospital admissions which included an ICU stay per annum was 7 (range: 0 to 19) in those aged 50 to 54 years, 8 (range: 0 to 19) in those aged 55 to 59 years, and 10 (range: 1 to 21) in those aged 60 to 64 years.
- influenza-related deaths per annum was 3 (range: 0 to 7) in those aged 50 to 54 years, 4 (range: 0 to 13) in those aged 55 to 59 years, and 6 (range: 0 to 13) in those aged 60 to 64 years.

- Hospital Inpatient Enquiry System (HIPE) data (which reflect the public acute hospital setting) showed substantial variability over time in relation to the number of discharges, length of stay (LOS) and total bed days over time. For those aged 50 to 64 years, data showed that between 2010 and 2022 (excluding 2020 and 2021 which are not representative due to the COVID-19 pandemic) there were, on average:
  - 199 (range: 17 to 571) discharges with a primary diagnosis of influenza per annum. The mean LOS was 6 days and the mean total bed days was 1,244 days per annum.
  - 19 (range: 7 to 40) discharges with a primary diagnosis of influenza that included an ICU stay per annum. The mean LOS was 14 days and the mean total bed days associated with these discharges was 314 days per annum.
  - 112 (range: 10 to 293) discharges with a secondary diagnosis of influenza per annum. 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 burden associated with influenza.

3.1 Introduction

This chapter describes the epidemiology of seasonal influenza and the burden of disease in Ireland, Europe and the UK amongst adults aged 50 to 64 years.

Influenza is a contagious respiratory illness. In many cases the disease is mild, with symptoms such as chills, fever and fatigue. Influenza can also result in serious complications, particularly in vulnerable people like young children, older adults (that is, those aged 65 years and older), pregnant women and people with medical conditions such as asthma, diabetes or heart disease.[7] Influenza viruses can be detected in most infected persons beginning one day before symptoms develop and up to five to seven days after becoming sick. 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 who are infected with influenza viruses may be contagious for longer than seven days.[53]

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. Virus immunity and the protection provided by vaccines is not life-long, making a large proportion of the population susceptible to infection each season.[9]

In the Northern Hemisphere, the influenza season commences in October and continues through to May. Influenza activity generally peaks during the winter season in 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.

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.[54] 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 Incidence of influenza in Ireland, Europe and the UK

The focus of this rapid 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, 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. Influenza surveillance involves collection of both clinical and virological data. Clinical surveillance monitors the impact of the illness on the health service and the community, while virological surveillance confirms that influenza is circulating and also identifies the current strain.[55]

3.2.1 Incidence of influenza in those aged 50 to 64 years in Ireland

Incidence of influenza in the community in Ireland is estimated from data obtained from the HSE's sentinel surveillance programme for influenza, one of several sentinel general practice surveillance programmes for infectious diseases in Ireland.[56] Influenza activity is monitored by season. The international surveillance period runs from October (week 40) to May (week 20) each year, although most countries including Ireland monitor influenza all year round.[55] 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 90 computerised general sentinel practices (located in all HSE-Areas) who report on a weekly basis the number of patients who consulted with acute respiratory infection (ARI) and or influenza-like illness (ILI). In this context, ILI is characterised by the sudden onset of symptoms 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.

The combined patient population in these sentinel general practices is estimated at 9-10% of the national population. Sentinel GPs send combined nose and throat swabs to the NVRL from ARI patients each week. The NVRL routinely test sentinel GP and non-sentinel respiratory specimens for influenza and a panel of other respiratory viruses.

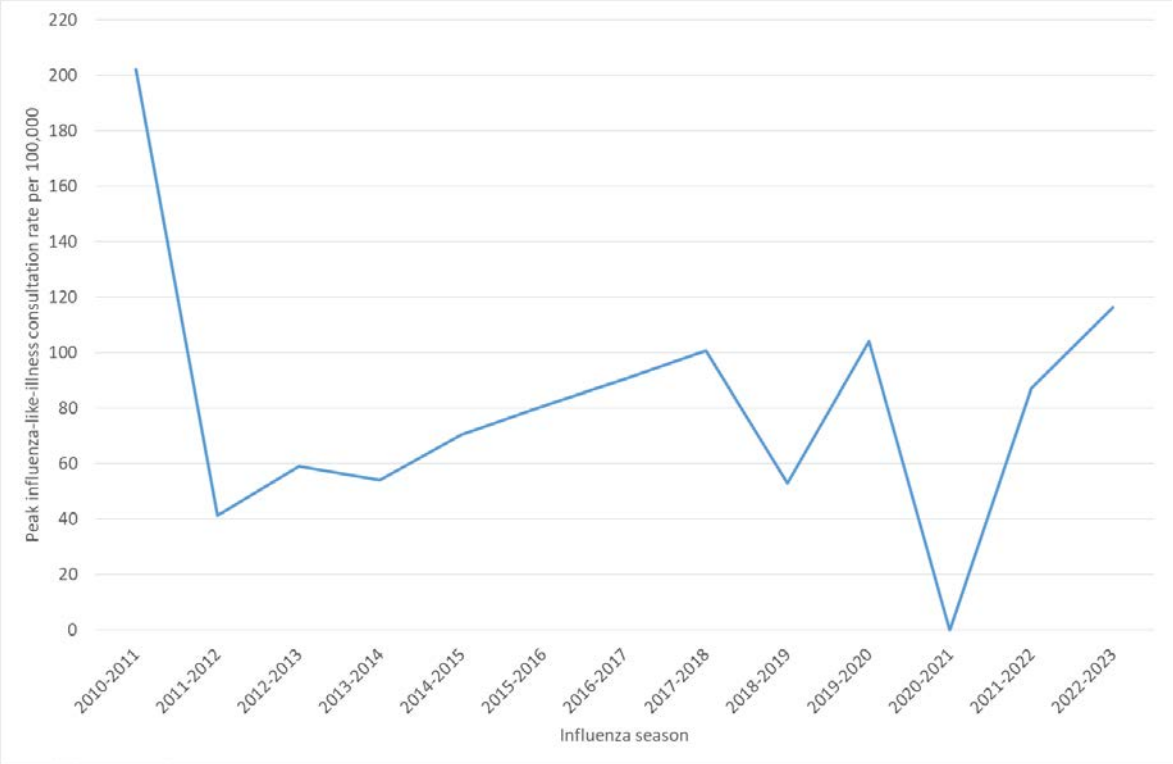
Other surveillance systems set up to monitor influenza activity include:

- surveillance of all confirmed influenza notifications, including hospitalisation status reported to the Computerised Infectious Disease Reporting System (CIDR) 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 centres, monitored for self-reported influenza and cough.
- all-cause excess mortality monitoring associated with the European mortality monitoring group
- acute respiratory infections and influenza outbreak surveillance.[55]

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 studies, cell culture and virus isolation.[55]

ILI and influenza data were gathered from the Sentinel GP network, Irish Computerised Infectious Disease Reporting system (CIDR) and the NVRL for 13 influenza seasons (2010-2011 to 2022-2023). Due to insufficient sample sizes for the target population, it was not possible to report the rates of ILI in those aged 50 to 64 years. However, data were reported for the peak ILI consultation rate per 100,000 for the total population (that is, all ages); these data are reported in Figure 3.1. For the most recent season (2022-2023 season), for which data are still incomplete, the peak ILI consultation rate was 116.2 per 100,000. While the peak ILI consultation rate typically ranges from 40 to 120 per 100,000 population, there are exceptions which include a high of 202.1 for the 2010-2011 season and a low of 0 in 2020-2021.

Figure 3.1 Peak influenza-like-illness consultation rate per 100,000 for the total population



Note: Data include all age groups. Data for the 2022-2023 flu season are incomplete.
Source: Health Protection Surveillance Centre.

Laboratory-confirmed influenza incidence rates per 100,000 for those aged 50 to 64 years are reported in Table 3.1. These data include those at increased risk of severe disease and are not specific to those in the general population. Data for the 2020-2021 and 2021-2022 seasons were clearly influenced by the COVID-19 pandemic, and are likely a poor representation of past and future incidence. 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 were 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 burden of influenza in the community setting as these cases represent a subset of those who attend the GP with influenza or ILI.

For the most recent season (2022-2023), for which data are at present incomplete, the notified influenza case rate per 100,000 was 256.9 (n=2,078), and the laboratory-confirmed influenza-related hospital admission rate was 67.3 (n=544), hospital admission with an ICU stay rate was 5.3 (n=43), and mortality rate was 2.1 (n=17); the estimated total number of cases in 50 to 64 year olds is also given in parentheses. Even excluding the seasons influenced by COVID-19 (2020-2021 and 2021-2022), there has been substantial variability in terms of the rates of notified influenza cases (range: 8.3 to 256.9) and laboratory-confirmed influenza-related hospital admissions (range: 1.8 to 75.2) in those aged 50 to 64 years. Similarly, there is evidence of variability in the rates of laboratory-confirmed influenza-related hospital admissions with an ICU stay (range: 0.3 to 6.1) and mortality (range: 0.0 to 3.6). In absolute numbers (and again excluding the seasons influenced by COVID-19), there has been substantial variability in the annual number of notified influenza cases (mean=738, range: 61 to 2,078), and laboratory-confirmed influenza-related hospital admissions (mean= 254, range: 13 to 608), hospital admissions with an ICU stay (mean=26, range: 2 to 49) and mortality (mean=12, range: 0 to 29) in those aged 50 to 64 years.

There appears to be a trend for increasing incidence of notified influenza cases from 2010 to 2022 in 50 to 64 year olds, and corresponding increases in laboratory-confirmed influenza-related hospital admission with or without an ICU stay, and mortality. However, it is unclear whether the trend for increasing incidence is solely due to increasing cases or if it is also influenced by increased testing and notification. The proportion of laboratory-confirmed influenza-related hospital admissions which include an ICU stay is static or declining over time, which may indicate that incidence is genuinely increasing. Caution is therefore required in inferring temporal trends based on the data presented in Table 3.1 given that it is presented as per 100,000 population.

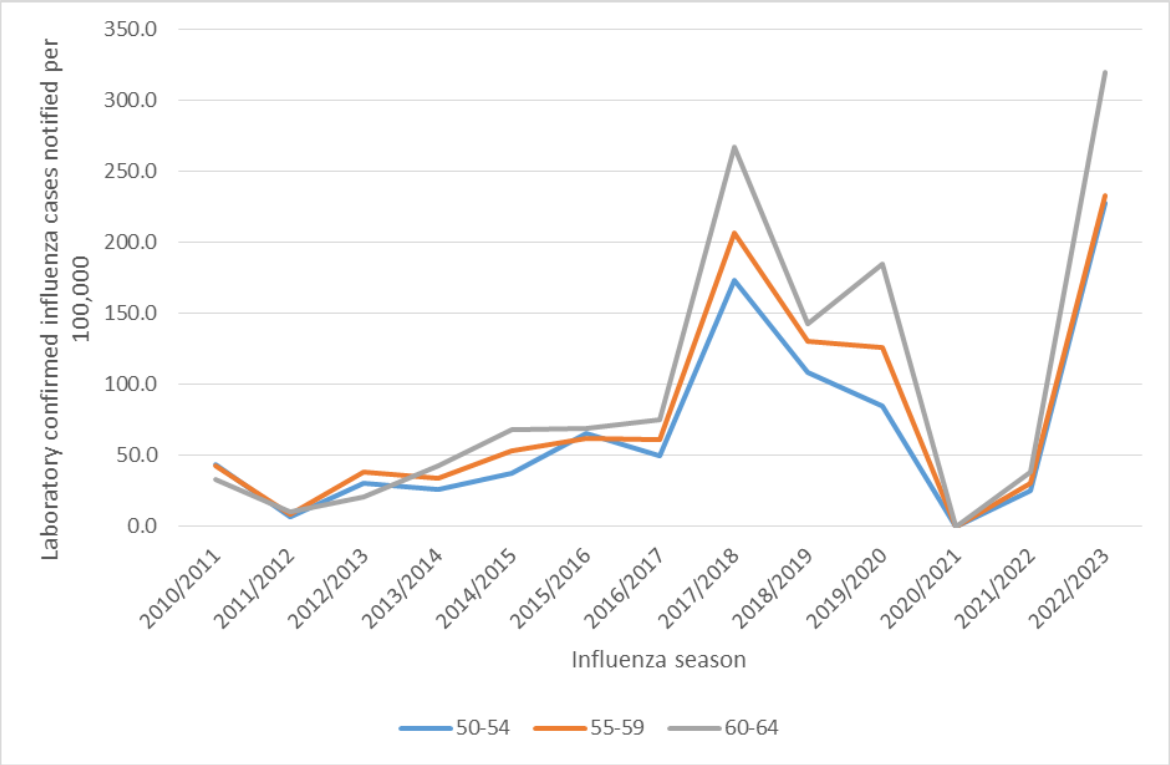
Table 3.1 Incidence rates of laboratory-confirmed influenza per 100,000 in those aged 50 to 64 years in Ireland

Season	Notified influenza cases	Influenza-related hospital admissions	Influenza-related hospital admissions which include an intensive care unit stay	Influenza-related mortality
2010 - 2011	40.1	20.6	6.1	2.6
2011 - 2012	8.3	1.8	0.3	0.0
2012 - 2013	30.4	5.6	0.7	0.1
2013 - 2014	33.6	13.3	2.0	0.9
2014 - 2015	51.4	13.8	1.1	0.6
2015 - 2016	65.4	27.1	6.1	3.6
2016 - 2017	61.1	22.0	1.1	0.5
2017 - 2018	212.3	75.2	5.1	3.0
2018 - 2019	125.7	51.8	5.6	2.0
2019 - 2020	128.2	49.2	2.3	1.9
2020 - 2021	0.0	0.0	0.0	0.0
2021 - 2022	30.7	6.2	0.5	0.5
2022 - 2023	256.9	67.3	5.3	2.1

Note: Data for the 2022-2023 flu season are incomplete.
Source: Health Protection Surveillance Centre.

The average number of notified influenza cases per annum was 231 (range: 19 to 684) in those aged 50 to 54 years, 242 (range: 20 to 629) in those aged 55 to 59 years, and 266 (range: 22 to 765) in those aged 60 to 64 years. The number of notified influenza cases per 100,000 per season for those aged 50 to 64 years are presented by five-year age band in Figure 3.2. To date, for the 2022-2023 season, the notified case rate is 228.0 (n=684) in those aged 50 to 54 years, 232.9 (n=629) in those aged 55 to 59 years, and 320.3 (n=765) in those aged 60 to 64 years. It should be noted that incidence in the 2022-23 season is the highest of the 13 seasons included in the data.

Figure 3.2 Number of notified influenza cases per 100,000 by five-year age band (for those aged 50 to 64 years) and season



Note: Data for the 2022-2023 flu season are incomplete.
Source: Health Protection Surveillance Centre.

3.2.2 Incidence of influenza in Europe and the UK

Since 2014, influenza surveillance in Europe has been jointly coordinated by the World Health Organization (WHO) Regional Office for Europe and the European Centre for Disease Prevention and Control (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).[57]

In the 2020-2021 influenza season, global influenza activity levels were extremely low. This was considered possibly attributable to the non-pharmaceutical interventions (that is, social distancing, restricted travel, hand hygiene and mask-wearing) recommended during the COVID-19 pandemic. As a result, population immunity against influenza was expected to be lower during the 2021-2022 influenza season.[58]

The Influenza Virus Characterisation Summary Report (WHO Europe), reports that as of week 8/2023, a total of 231,015 influenza detections had been reported, of which

21,064 were from sentinel sources. For the 2021-2022 season, the number of influenza detections within the same time period were 44,665 (of which 2,546 were from sentinel sources). This represents a 5.2-fold increase in detections for the 2022-2023 season, despite there being a 4% decrease in the number of samples tested. Decreased detections during the 2021-2022 season may be attributable to reduced spread of influenza viruses due to implementation of non-pharmaceutical interventions (such as, social distancing and hand hygiene) in the context of the COVID-19 pandemic, and or patients not attending their GP.

In EU/EEA countries seasonal influenza viruses are estimated to cause up to 50 million symptomatic infections each year.[9] While consultation rates for influenza-like illness with positivity for influenza, COVID-19 and respiratory syncytial virus (RSV) are included, disaggregated data specifically for those aged 50 to 64 years old are not included in the reports.

In the UK, influenza activity is monitored through a variety of primary and secondary care schemes. The UK Health Security Agency collates weekly reports with additional information for Northern Ireland provided by the Public Health Agency, for Wales by Public Health Wales, for Scotland by Public Health Scotland and for England by the Royal College of General Practitioners. Disaggregated data specifically for those aged 50 to 64 years old are not included in the published reports.

3.3 Burden of disease

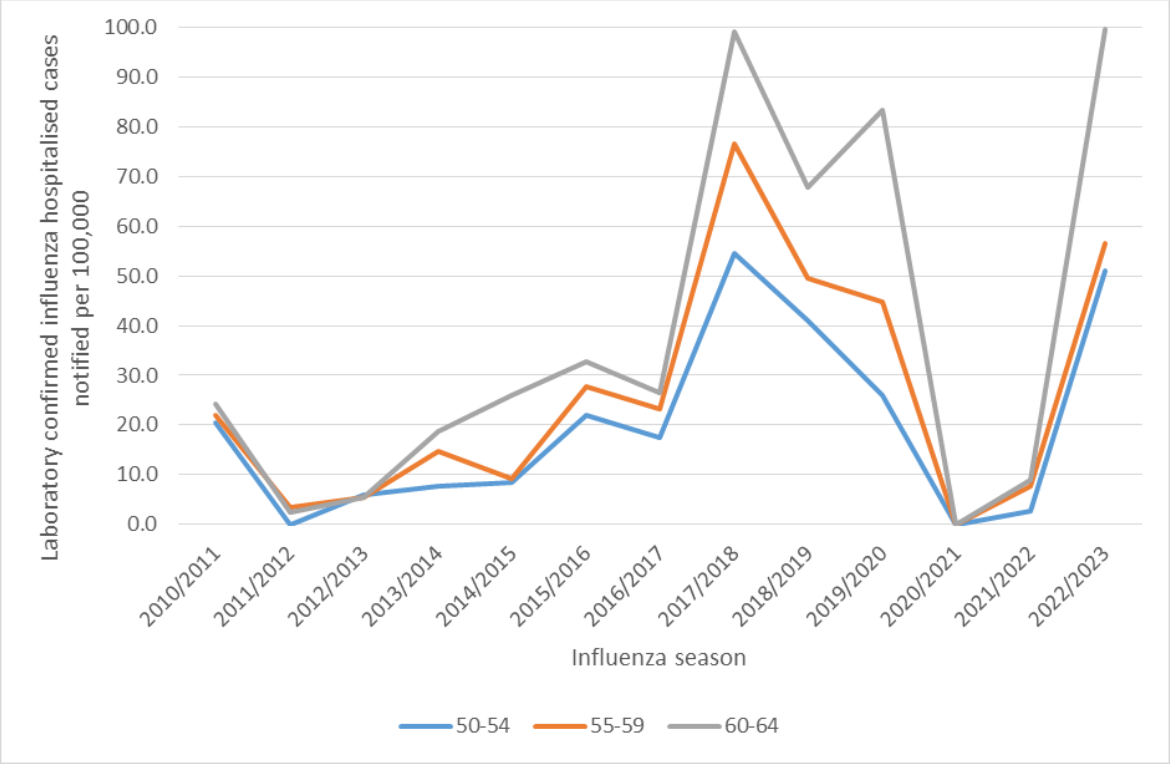
There is a dearth of data relating to the burden of disease for the target population (that is, those aged 50 to 64 years and not at increased risk of severe disease).[59] Differences in burden by age are noted. In the annual epidemiological report for seasonal influenza 2021-2022, the ECDC reported that in laboratory-confirmed influenza cases in ICU (France, Sweden, Ireland and Czechia reported hospitalisation data) the majority of severe cases occurred in those aged 60 to 79 years (41.5%), followed by those aged 0 to 19 years (22.9%), 40 to 59 years (18.4%), 20 to 39 years (11.1%) and those aged 80 and over (6.1%). However, it is noted that these results are for the total population and do not exclude those considered to be at increased risk of severe disease.

3.3.1 Complications and hospitalisations

The average number of laboratory-confirmed influenza-related hospital admissions per annum was 69 (range: 0 to 164) in those aged 50 to 54 years, 81 (range: 8 to 207) in those aged 55 to 59 years, and 105 (range: 5 to 238) in those aged 60 to 64 years. The total number of laboratory-confirmed influenza hospitalised cases per 100,000 in Ireland from 2010 to 2022 are reported for those aged 50 to 64 years in Figure 3.3; these data were provided by the HPSC and are reported according to

influenza season and disaggregated by five-year age band. Within the 50 to 64 year old group, the rate of laboratory-confirmed influenza hospitalisation was generally highest in the subgroup aged 60 to 64 years. To date, for the 2022-2023 season, the notified hospitalised case rate is 51.0 (n=153) in those aged 50 to 54 years, 56.6 (n=153) in those aged 55 to 59 years, and 99.6 (n=238) in those aged 60 to 64 years. These data include admissions in those identified to be at increased risk of severe disease.

Figure 3.3 Total number of laboratory-confirmed influenza hospitalised cases per 100,000 by five-year age band (for those aged 50 to 64 years) and season in Ireland

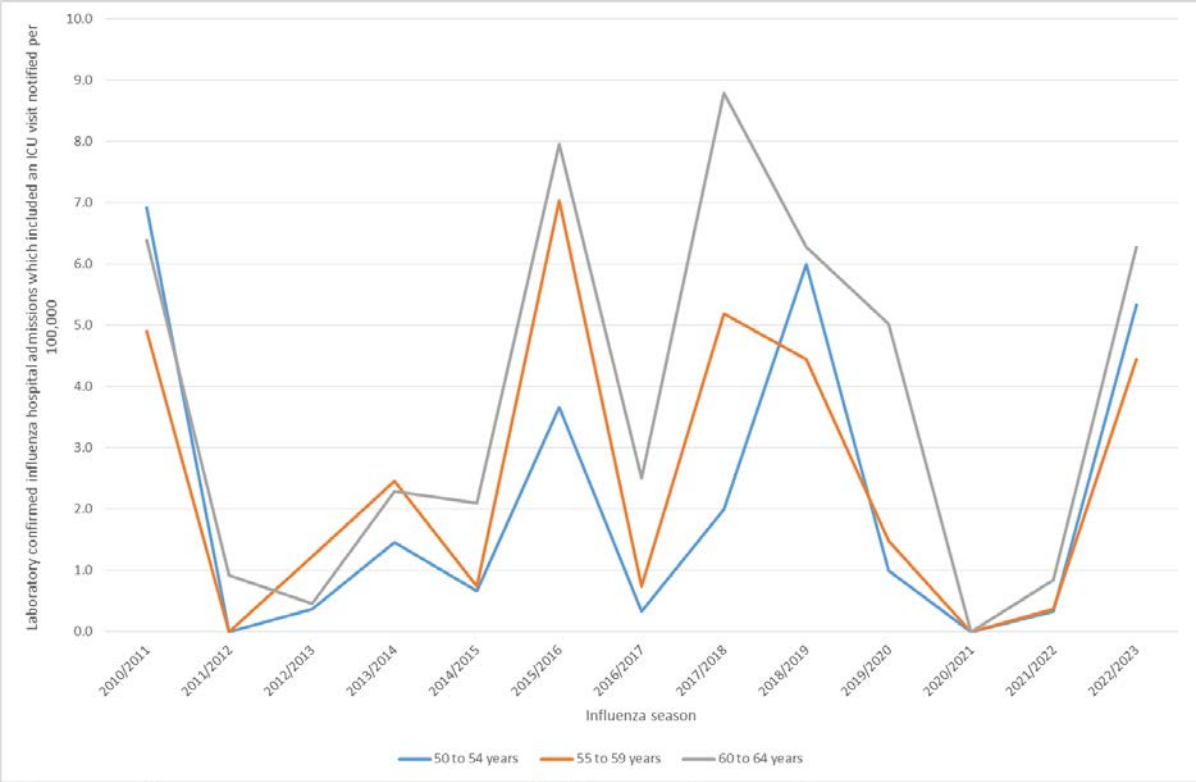


Source: Health Protection Surveillance Centre.

HPSC data were used to report the number of laboratory-confirmed influenza hospital admissions which included an ICU stay. The average number of laboratory-confirmed influenza-related hospital admissions which included an ICU stay per annum was 7 (range: 0 to 19) in those aged 50 to 54 years, 8 (range: 0 to 19) in those aged 55 to 59 years, and 10 (range: 1 to 21) in those aged 60 to 64 years. From 2010-2022, the number of laboratory-confirmed influenza hospital admissions which included an ICU stay per 100,000 notified in Ireland from 2010 to 2022 are reported by five-year age band in Figure 3.4. There was evidence of year-on-year variation in the rates of hospital admissions which included an ICU stay, although typically, rates were higher in those aged 60 to 64 years. To date, for the 2022-2023

season, the rate (per 100,000) of laboratory-confirmed influenza-related hospital admissions which include an ICU stay is 5.3 (n=16) in those aged 50 to 54 years, 4.4 (n=12) in those aged 55 to 59 years, and 6.3 (n=15) in those aged 60 to 64 years.

Figure 3.4 Total number of laboratory-confirmed influenza hospital admissions which include an intensive care unit stay per 100,000 by five-year age band (for those aged 50 to 64 years) and season in Ireland



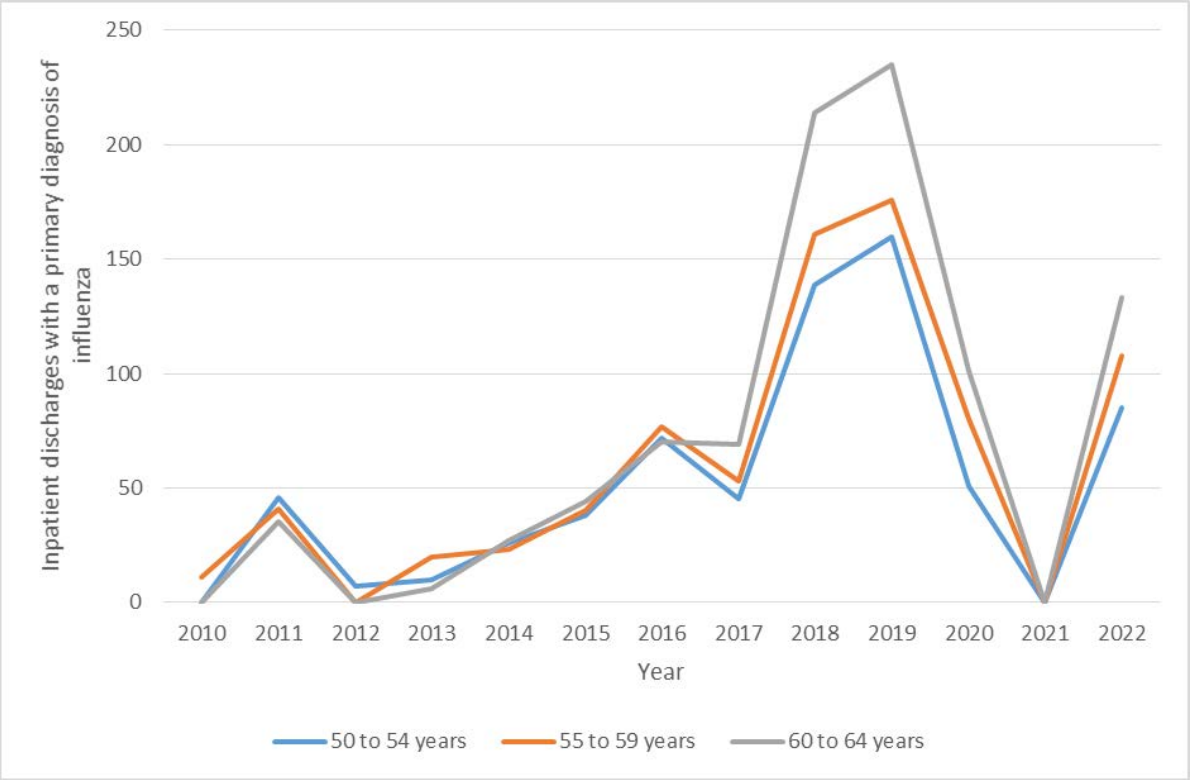
Source: Health Protection Surveillance Centre.

Data from the Hospital Inpatient Enquiry System (HIPE) in Ireland was used to examine hospital discharges with and without an ICU stay for patients aged 50 to 64 years with a primary or secondary diagnosis of influenza and or upper respiratory infections with ICD-10 codes J09, J10 and J11. These data were provided for the total age group aged 50 to 64 years, so include hospitalisations in those identified as being at increased risk of severe disease. Data were provided by calendar year rather than by flu season, so may not fully capture changes in disease severity across seasons.

Excluding the years 2020 and 2021 (which are not considered representative due to the influence of COVID-19), a total of 2,193 discharges with a primary diagnosis of influenza were reported from 2010 to 2022. This equated to an annual average of 199 (range: 17 to 571) discharges with a primary diagnosis of influenza. Over the

12-year period, the number of discharges with a primary diagnosis of influenza were similar across the three five-year age bands. However, during the two years with the highest influenza rates (2018 and 2019), the differences between the age bands appears more pronounced; that is, there were more discharges in those aged 60 to 64 years (Figure 3.5).

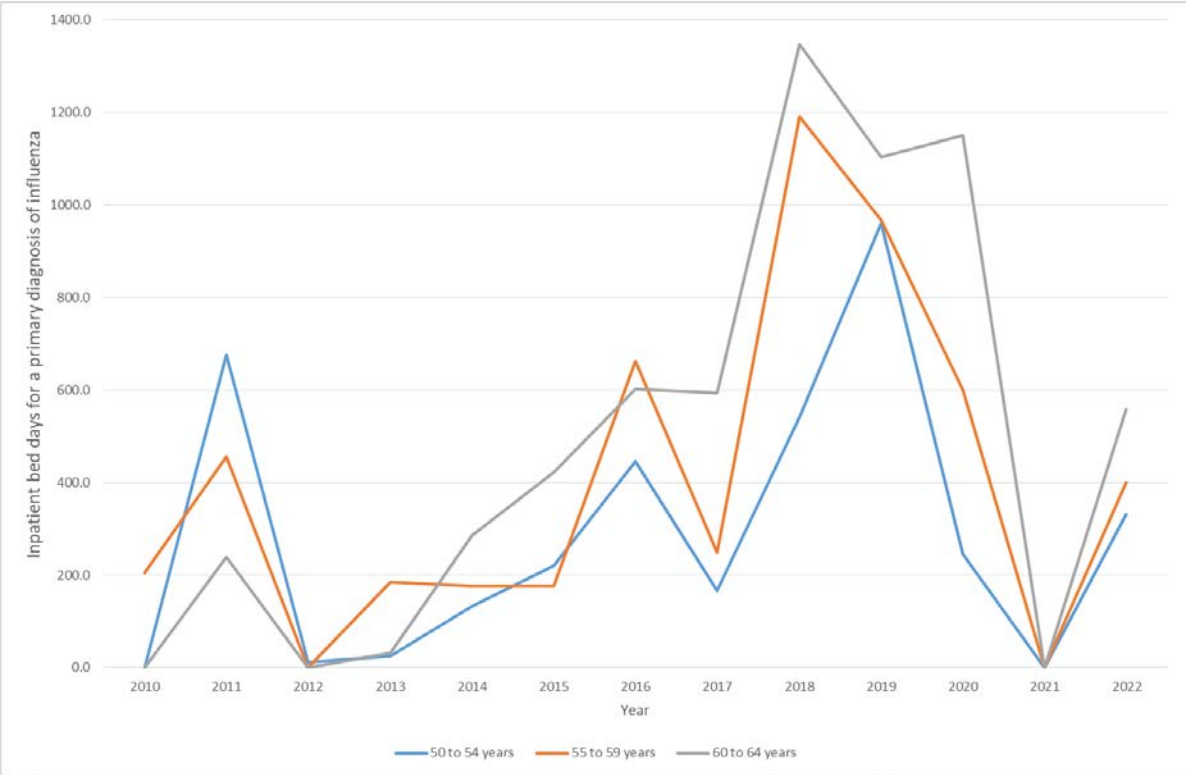
Figure 3.5 Total inpatient discharges from acute hospitals aged 50 to 64 years (by five-year age band), with a primary diagnosis from the specified list of influenza diagnosis codes



Source: Hospital Inpatient Enquiry System.

Again, excluding the years 2020 and 2021, using HIPE data, the median length of stay in hospital for those with a primary diagnosis of influenza varied between one and six days. The mean length of stay was 6 days and the mean total bed days per annum was 1,244 days. Given the variation in the hospital discharge rate over the 12 year period, there was also evidence of variation in total bed days, ranging from 53 in 2012 to 3,084 in 2018 (Figure 3.6). When disaggregated by five year age band, total bed days were typically higher in those aged 60 to 64 years.

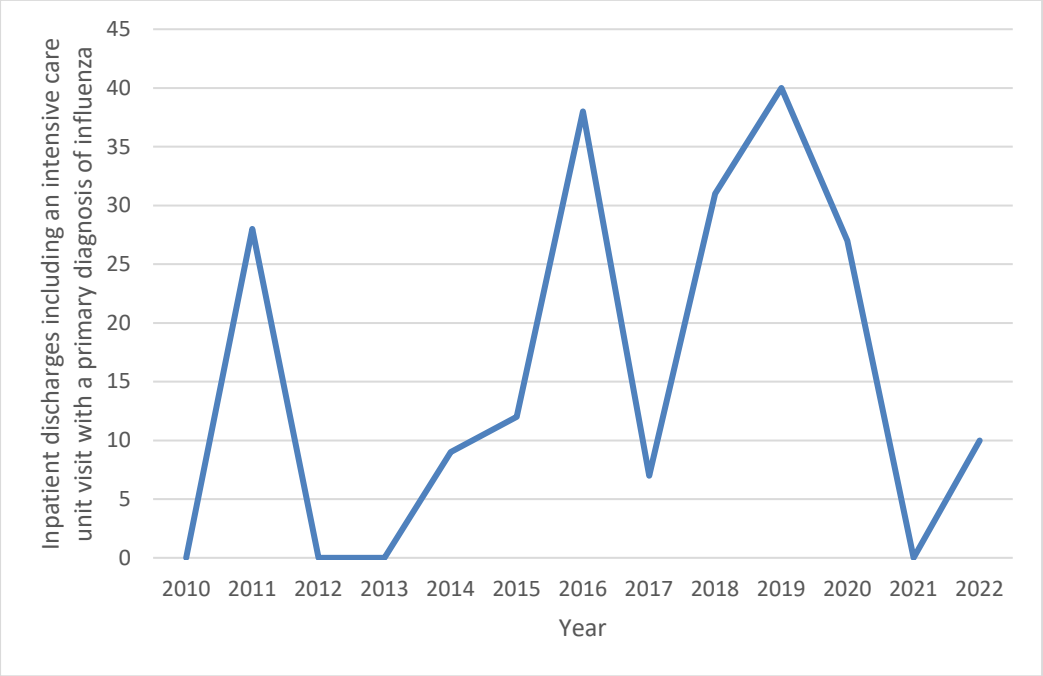
Figure 3.6 Total inpatient bed days for those aged 50 to 64 years, with a primary diagnosis from the specified list of influenza diagnosis codes reported by five-year age band



Source: Hospital Inpatient Enquiry System.

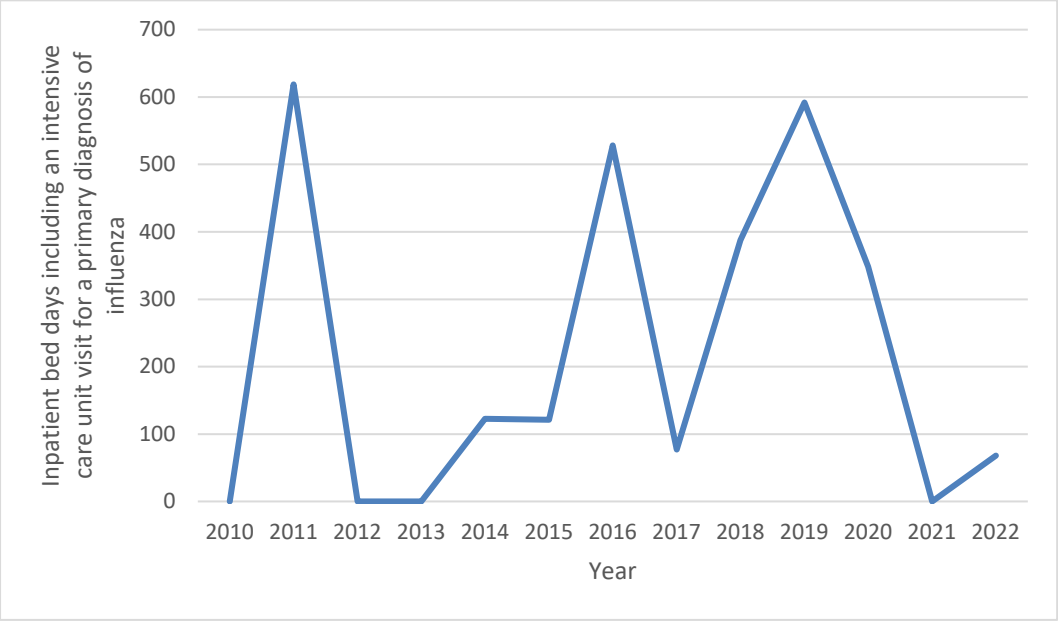
In those aged 50 to 64 years, there were a total of 175 hospital discharges that included an ICU stay for those with a primary diagnosis of influenza from 2010 to 2022 (excluding the years 2020 and 2021 due to the influence of COVID-19). This equated to an annual average of 19 (range: 7 to 40) discharges that included an ICU stay. There was considerable year-on-year variation, ranging from fewer than five discharges in 2010, 2012 and 2013 to 40 discharges in 2019 (note these data are reported according to calendar year not influenza season); see Figure 3.7. For these discharges, the median total length of hospital stay (which included an ICU stay) fluctuated between four and 17.5 days. The mean length of stay was 14 days and the mean total bed days per annum was 314 days. It should be noted that due to small numbers, the total inpatient length of stay can be heavily influenced by one or a small number of patients with a long length of stay. Figure 3.8 depicts the total bed days (including an ICU stay) associated with influenza each year in those aged 50 to 64 years as reported by HIPE. It was not possible to report these data disaggregated by five-year age band.

Figure 3.7 Total inpatient discharges from acute hospitals which included an intensive care unit stay for those aged 50 to 64 years, with a primary diagnosis from the specified list of influenza diagnosis codes



Source: Hospital Inpatient Enquiry System.

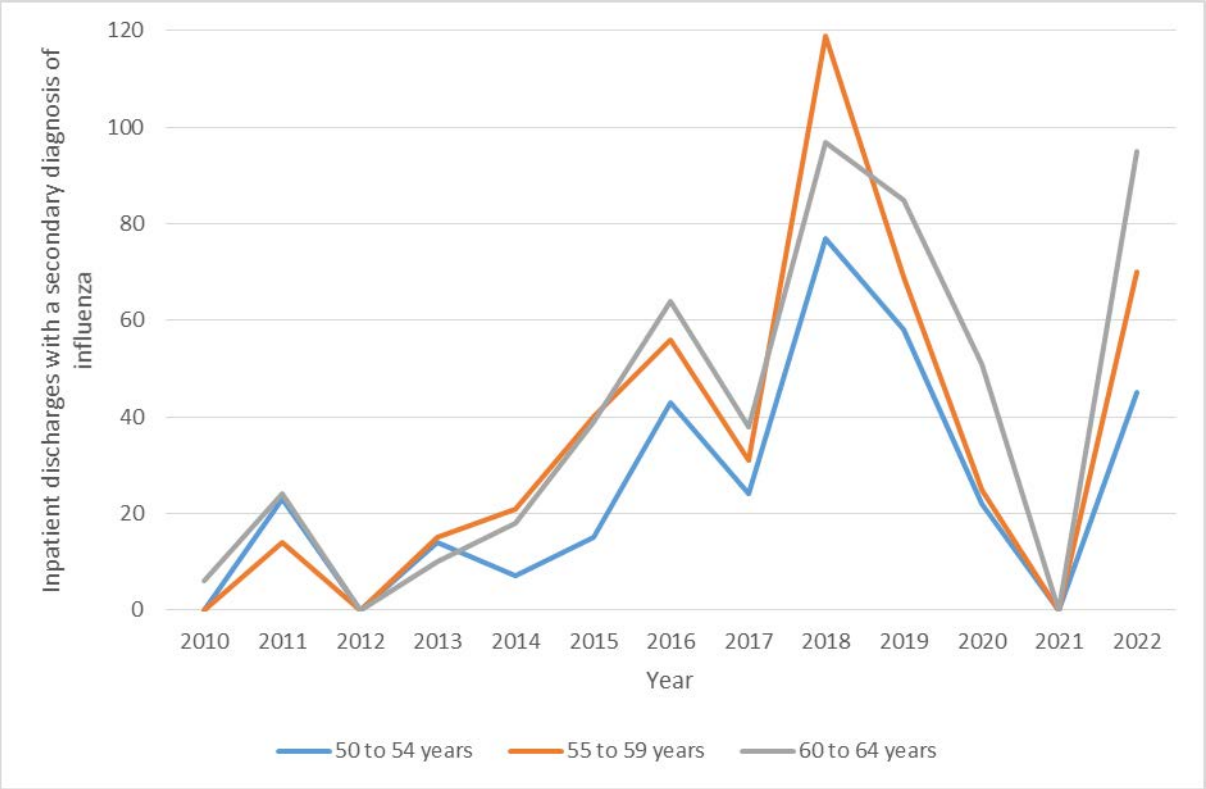
Figure 3.8 Total inpatient bed days which included an intensive care unit stay for those aged 50 to 64 years, with a primary diagnosis from the specified list of influenza diagnosis codes



Source: Hospital Inpatient Enquiry System.

A total of 1,235 discharges with a secondary diagnosis of influenza were reported from 2010 to 2022 in those aged 50 to 64 years. This equated to an average of 112 (range: 10 to 293) discharges per year. When disaggregated by five-year age band, with the exception of 2011, the number of discharges with a secondary diagnosis of influenza was consistently lowest in those aged 50 to 54 years (Figure 3.9). Data on the average length of stay in hospital for those with a secondary diagnosis of influenza were not reported.

Figure 3.9 Total inpatient discharges from acute hospitals with a secondary diagnosis from the specified list of influenza diagnosis codes reported by five-year age band



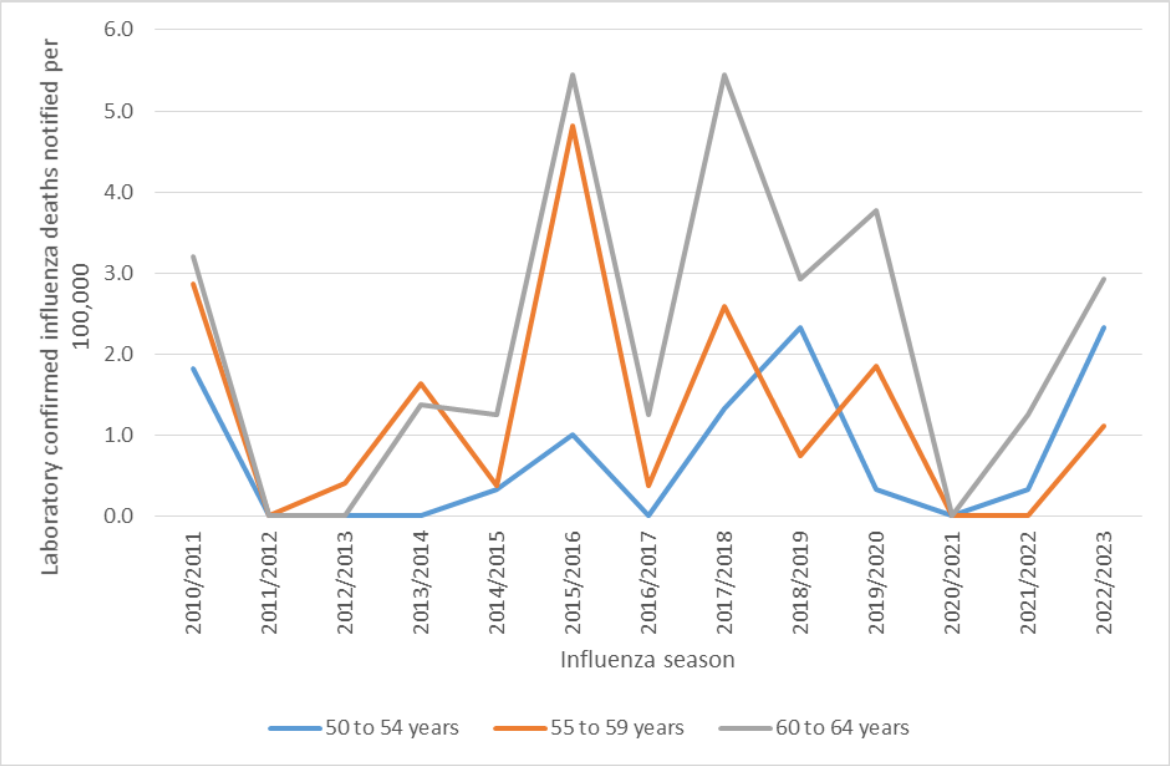
Source: Hospital Inpatient Enquiry System.

3.3.2 Mortality

Most patients experience uncomplicated illness, but some develop severe disease which can be characterised by exacerbation of chronic medical conditions, acute respiratory distress syndrome, severe pneumonia, sepsis and potentially lead to death.[60] Influenza-related mortality data were obtained from the HPSC. The average number of laboratory-confirmed influenza-related deaths per annum was 3 (range: 0 to 7) in those aged 50 to 54 years, 4 (range: 0 to 13) in those aged 55 to 59 years, and 6 (range: 0 to 13) in those aged 60 to 64 years. Data on mortality rates per 100,000 are presented in Figure 3.10 by five-year age band). The data

indicate substantial year-on-year variability, although typically higher mortality rates were observed with increasing age. While the data for the 2022-2023 season are incomplete, the most recent data indicate a laboratory-confirmed influenza-related mortality rate of 2.3 (n=7) in those aged 50 to 54 years, 1.1 (n=3) in those aged 55 to 59 years, and 2.9 (n=7) in those aged 60 to 64 years. Again, these data are not disaggregated according to risk status (that is, they may include data for individuals considered to be at increased risk of severe disease).

Figure 3.10 Number of laboratory-confirmed influenza-related deaths per 100,000 notified by five-year age band (for those aged 50 to 64 years) and season in Ireland



Source: Health Protection Surveillance Centre.

3.3.3 Burden of disease internationally

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. These data are not disaggregated for the 50 to 64 year age group.[61]

A 2022 UK surveillance report indicated that in secondary care, for both hospital and critical care for the majority of the season, influenza admissions remained below the baseline threshold. Although rates were higher than observed in the 2020-2021 season, they were lower than those seen in previous seasons. The cumulative

hospitalisation admission rate for the 2021-2022 season (between week 40 and week 14) was 5.84 per 100,000 hospital trust catchment population. This compares with rates of 0.18, 44.03, 45.33 and 76.20 per 100,000 for the preceding four flu seasons (2020-2021, 2019-2020, 2018-2019, 2017-2018), respectively; these data were not disaggregated by age.[62]

A 2021 review including 20 studies from 13 countries reported the burden of severe illness associated with laboratory-confirmed influenza in adults aged 50 to 64 years. The studies reported hospitalisation and or mortality rates among adults 50 to 64 years or 45 to 64 years for the influenza seasons 2010-2011 through 2019-2020. Hospitalisation rates ranged from 5.7 (Portugal, 2013 to 2014) to 112.8 (United States, 2017-2018) per 100,000 with an average of 56.7 per 100,000 for the 2010-2011 to 2019-2020 seasons. Only one study reported mortality rates, which ranged from 0.8 to 3.5 per 100,000 over four seasons. Among those hospitalised with influenza, the case fatality rate ranged from 1.3% to 5.6%. The researchers concluded that there is a significant burden of morbidity for those aged 50 to 64 years due to seasonal influenza. It is noted that the data were not specific to the general population and likely included individuals identified to be at high risk of severe disease. Few of the studies included in the review reported on risk factors for death and severe outcomes; indeed, these risk factors may vary between countries and may impact the variation in hospitalisations and mortality observed.

A Spanish study comprising data from ten influenza epidemic seasons (2008/2009-2017/2018 (excluding data for HINIpdm09 pandemic (2009/10)) estimated the clinical and economic burden of severe influenza measured through hospitalisations and deaths. 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. For those aged 50 to 64 years the mean annual number of hospitalisations was 24.8 per 100,000, the rates for those aged 0 to 4 years, 5 to 18 years, 19 to 49 years, 65 to 74 years and 75 years and older per 100,000 were (61.1, 8.4, 7.4, 51.7 and 123.8, respectively). Mean length of stay (LOS) differed by age group and depended on the presence or absence of comorbidities. Across all seasons, overall mean LOS was 9.4 days (range: 6.6 – 11.4 days) and was highest in those aged 50 to 64 years (mean: 11.7 days; range 7.8 to 14.8). In those aged less than 65 years, mean LOS was higher in those with compared to those without comorbidities at 12.0 (range: 7.1 to 15.1) versus 6.9 (range: 4.9 to 9.2).[63]

A 2022 study sought to estimate the epidemiological and economic burden of severe influenza over eight seasons (2010-2018) in France.[64] Analysis of hospitalisations represents data for 2010-2018 and analysis of mortality represents data for 2010-2015 and both were stratified by age group. Results indicated that the annual

average rate of hospitalisation was 28 per 100,000. The proportion of transfer to ICU ranged from 0.0 (range: 0.0-0.1) for those aged 0 to 4 years to 23.1 (range: 18.2-26.9) for those aged 50 to 64 years; those aged 65 years and older accounted for 80% of in-hospital deaths due to influenza. The median LOS for those aged 50 to 64 years was seven days, compared to four days for those aged 20 to 49 years, three days for those aged 0 to 4 years and 10 days for those aged 85 years and older. The age group with the highest total cost over the study period (during low and middle-intensity epidemic seasons) was those aged 50 to 64 years (€9.1 million) with those aged 5-19 years accounting for the lowest cost (€2.8 million). In severe epidemic seasons, those aged 65 years and older accounted for more than 67% of the total cost, with an average of €98.3 million.

NHS England reported that cases of influenza in hospital in the week leading up to New Year's day 2023 increased by 47% on the previous week (from 3,479 to 5,105 patients).[62] The number of patients with influenza in critical care beds increased from 267 to 336 (an increase of 26%) over the same week. For the same week the previous year, there were two patients in critical care beds and 38 cases in hospital.[65] A 2016 UK study noted that 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.[66]

3.4 Vaccination against influenza

Vaccination can offer protection against seasonal influenza by preventing transmission and or reducing its impact as well as preventing onward transmission to others. Annual vaccination is required because of waning immunity and also because influenza strains 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.[67] Figures from the US Centers for Disease Control and Prevention show that adjusted overall vaccine effectiveness ranged from 19% to 60% for the flu seasons 2009-2010 to 2021-2022.

3.4.1 Uptake of influenza vaccination in Ireland amongst adults aged 50 to 64 years

Historical uptake rates for influenza vaccination in Ireland were obtained from the HPSC. These figures reflect the administration of influenza vaccines reimbursed through the HSE's Seasonal Influenza Vaccination Programme and include data across all settings: GP practices, community pharmacies, long term care facilities and hospitals. In those aged 50 to 64 years, the uptake rate was estimated at

approximately 26.5% (n=233,034) and 30.2% (n=270,785) for the 2021-2022 and 2022-2023 influenza seasons, respectively.[68] Of note, these uptake rates reflect uptake in the total population rather than as a proportion of those eligible through the programme.While reimbursement for those aged 50 to 64 years within the programme has typically been limited to defined groups (for example, healthcare workers and those identified as being at increased risk of severe disease), data for the 2021-2022 season included the target population (that is, those aged 50 to 64 years and not at increased risk of severe disease) due to the temporary extension of the influenza programme. Of note also, these uptake data are an underestimate of total uptake in this age group as they do not include uptake outside the HSE programme, for example, where individuals or an employer (as part of an occupational health scheme) pay for the vaccine privately.

3.4.2 Uptake of influenza vaccination in the UK and Europe amongst adults aged 50 to 64 years

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.[69] The most recent report, based on survey data gathered in January 2018 indicated differences in vaccination coverage across countries. These data were reported separately for healthcare workers, those with chronic medical conditions, pregnant women, residents of long-term care facilities and older age groups (this was variably defined as age ≥55, ≥59, ≥60 or ≥65 years). No disaggregated data for the population aged 50 to 64 years were reported.[40]

In England, on 1 December 2020, those aged 50 to 64 years and not at increased risk of severe disease became eligible for the influenza vaccine.[70] For the 2020-2021 influenza season, uptake of the vaccine by this group was 35.2% of the population. However these data were taken from general practice systems only and therefore did not capture vaccination in other settings by other healthcare providers (for example, pharmacies, schools and special clinics). In the subsequent year, on 1 September 2021, this group was again included in the influenza vaccination programme and uptake for the 2021-2022 season was 45.7%. These percentages are not directly comparable as the start dates of eligibility differed. In considering uptake rates for those aged 50 to 64 years regardless of their risk status, data suggest that influenza vaccination uptake was 52.5% (for the 2021-2022 season) and 45.2% (for the 2020-2021 season).[70] Of note, the 2021-2022 annual influenza letter stated that the aim was to achieve a vaccination rate of 75% in those aged 50 to 64 years (regardless of risk status).[58] For the 2022-2023 influenza season, all categories of eligible vaccination recipients, including those aged 50 to 64 years and not at increased risk of severe disease, saw a decrease in vaccine uptake, when

compared to the previous influenza season. Uptake in those aged 50 to 64 years and not at increased risk of severe disease decreased from 45.7% to 40.6%.[71]

While general practice is the main healthcare setting through which patients receive influenza vaccinations in the UK, there has been a gradual increase in vaccinations administered in pharmacies and other healthcare settings. After general practice, the highest percentage of influenza vaccinations are administered in pharmacies. In those aged 50 to 64 years and not at risk of severe disease (for the 2021-2022 season), 49.2% of influenza vaccines were given in general practice, 39.1% were given in pharmacies, and 11.7% were given in other healthcare settings. For the 2020-2021 season, the percentages of influenza vaccination administration in general practice, pharmacies and other healthcare settings were 69.3%, 24.5% and 6.2%, respectively.

From 11 of January 2021 the influenza vaccination programme of Northern Ireland was extended to include those aged 50 to 64 years. The rationale for this expansion was to relieve pressure on the health service and help protect more people from the virus. The vaccine was delivered through local GP practices or from over 350 community pharmacies.[72] The seasonal influenza campaign for 2022 to 2023 in Northern Ireland started on 19 September 2022 and finished on 31 March 2023.[73] On 19 January 2023, the Public Health Agency stated that 50.4% uptake was achieved in the 50 to 64 years age group, representing an increase of 10% on the previous year's uptake (2021-2022 season). However, there was no indication as to what proportion of this age group were at increased risk of severe disease.[74]

The Scottish Government first announced the expansion of free influenza vaccination to those over 55 years of age in August 2020.[75] For the following influenza 2021-2022 season, those aged 50 years and older were also included and this has continued for the 2022-2023 season.[75] As noted in the 6 April 2023 (final update) Public Health Scotland Flu Vaccination Dashboard, for the 2022-2023 winter vaccination programme, 55.4% of those aged 50 to 64 years (unclear if this includes the at risk population) who are recorded within the Community Health Index database received the influenza vaccine (n=677,150).[76]

In July 2020, the Welsh Government announced the extension of their influenza vaccination programme to include otherwise healthy individuals aged 50 to 64 years on a phased basis and on the proviso that those in existing eligible groups would take priority.[77] These individuals were included in the programme for the 2021-2022 season and again in the 2022-2023 season. In June 2023, a decision was taken to revert to the age eligibility that applied before the COVID-19 pandemic, that is, that otherwise healthy individuals aged 50 to 64 years would no longer form part of the eligible cohort.[78]

As of 13 December 2022, community pharmacies in Wales had vaccinated 152,593 people for the 2022-2023 season. Over 168,000 vaccinations were recorded as administered towards the end of 2021, indicating a decrease in uptake in the community pharmacy setting from 2021 to 2022.[79]

In the UK the aim for the 2023-2024 season is to achieve a global vaccine uptake rate for COVID and influenza of 75%. With regard to those aged 50 to 64 years, while the UK's Joint Committee on Vaccination and Immunisation (JCVI) considered that vaccinating the 50 to 64 years age group (regardless of risk status) would provide a clear health benefit, there was uncertainty as to whether it would meet strict cost effectiveness criteria sufficient to divert from more cost-effective interventions.[80] As such, as of May 2023, the UK government has reversed their decision on reimbursing influenza vaccination of those aged 50 to 64 years and not at increased risk of severe disease.

Influenza vaccination uptake rates in those countries offering reimbursement of influenza vaccination for all or part of the target population (as outlined in Chapter 2, Table 2.2) are difficult to identify. Uptake data were not identified for the majority (Germany, Greece, Hungary, Iceland, Malta and Slovakia) of these countries. In the Netherlands, influenza vaccine uptake figures were identified for those aged 60 to 64 years and without a medical indication for vaccination. These data are reported by General Practices participating in the Nivel Primary Care Database. The data suggest that 26.8% of the population (aged 60 to 64 years and without a medical indication for vaccination) were vaccinated against influenza in 2018[81] increasing to 34.9% in 2020.[82]

3.5 Economic burden of influenza

Influenza places a large economic burden on society and healthcare systems internationally.[83] In considering the economic burden associated with influenza, both direct and indirect costs are relevant.[84] Direct costs include those related to providing care for the patient, for example, primary care visits, medication costs and hospitalisation costs.[85] Indirect costs include productivity losses due to illness, disability related to consequential conditions of the disease, or premature death.[85] 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.[9] 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.

Within the context of this rapid HTA, a brief overview of relevant literature was undertaken. No data specific to Ireland were identified.

A Spanish study carried out in 2022 explored the cost of illness for medically-attended influenza cases in adults aged 18 years or older. Data related to influenza cases diagnosed during the 2017-2018 season were sourced from the National Healthcare Service in four regions of Spain. Most patients in the study were aged 18 to 49 years (60.5%), 26.3% of cases were aged 50 to 64 years and 13.3% were aged 65 years and older. Among those who visited a healthcare setting, mean healthcare costs per case differed by age group, with mean costs estimated at €402 for those aged 50 to 64 years compared with €235 for those aged 18 to 49 years and €1,149 for those aged 65 years and older. For those aged 50 to 64 years, mean healthcare costs were primarily driven by hospitalisations (4.1% of those diagnosed) and primary care (98.8% of those diagnosed), 71% of healthcare costs in this age group were attributable to patients with comorbidities. The proportion of healthcare costs attributable to different care settings differed in patients with and without comorbidities (for example, 35.8% primary care and 51.8% hospital inpatient versus 75.0% primary care and 10.9% hospital inpatient in those age 50 to 64 years with and without comorbidities).[86]

Two industry-sponsored UK studies examined the potential impact of administering a cQIV to those aged 50 to 64 years and not at increased risk of severe disease, compared with not vaccinating this group.[87, 88] The studies concluded that vaccination would be cost effective or potentially cost saving due to a reduction in GP visits, hospitalisations and mortality associated with influenza.[87, 88] Due to the risk of bias and the use of cQIV instead of standard QIV, the results of these studies are of unclear applicability.

3.6 Discussion

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 in Europe as a result of influenza-associated causes.[9] During the influenza season all age groups are affected, although proportions vary from one year to another, depending on population immunity and dominating viruses.

With respect to Ireland, data were gathered from the Sentinel GP network, CIDR and NVRL for the total population aged 50 to 64 years from the 2010-2011 season to the 2022-2023 season; these data were also disaggregated by five-year subgroups. Data reported in this rapid HTA show some evidence of a trend for increasing incidence of influenza from 2010 to 2022 in 50 to 64 year olds, and corresponding increases in hospital admission with or without an ICU stay, and mortality. It is noted that these data include the total population aged 50 to 64 years and therefore include individuals considered to be at elevated risk of severe disease

as well as those with underlying conditions that increase their risk of severe disease but are undiagnosed. Multimorbidity (the presence of two or more long term conditions) is strongly associated with increasing age.[89] In a population study conducted in Ireland, the population-weighted prevalence of multimorbidity in a representative sample of over 6,000 adults aged 50 years or older was 73.3%.[90] Data from the HPSC show that rates of notified influenza cases, laboratory-confirmed influenza-related hospital admissions with or without an ICU stay and deaths were higher in those aged 60 to 64 years compared with those aged 50 to 54 years, and those aged 55 to 59 years (for the 2022-2023 season). The increasing prevalence of multimorbidity with age may contribute to the increased risk of severe influenza and associated hospital admission with or without an ICU stay and mortality in those aged 60 to 64 years. However, while there are differences in the rates of influenza cases and outcomes across the three age bands, it is unclear whether vaccination would result in substantial benefits for one subgroup over another.

Additionally, this rapid HTA includes pre and post COVID-19 data. There is evidence to suggest that co-infection with SARS-CoV-2 and influenza may be associated with an increased risk of complications. A study in the UK examined the clinical outcomes in adults admitted to hospital with SARS-CoV-2 infection.[91] Viral co-infection was detected in 583 (8.4%) patients, of which 227 patients had co-infection with influenza viruses. Extrapolated results (from the tested population to a representative hospitalised population) showed that co-infection with influenza and SARS-CoV-2 was associated with an increased risk of mechanical ventilation (odds ratio (OR) 4.14 (95% confidence intervals (CI) 2.00–8.49)), and death (OR 2.35 (95% CI 1.07–5.12)). While COVID-19 is no longer considered a public health emergency of international concern, there is a potential for higher burden on secondary care services given the continued circulation of SARS-CoV-2, the potential for new variants of concern and or waning of population immunity.

While influenza vaccination can reduce the burden of influenza both through direct protection and prevention of onward transmission, vaccine effectiveness varies from year to year; data from the US Centers for Disease Control and Prevention suggesting that adjusted overall vaccine effectiveness has ranged from 19% to 60%. Causes of this variation include variability in the virus types and subtypes in circulation, the virulence of those types, and the degree of matching between the circulating strain and the content of the seasonal vaccine.[67] This variation in effectiveness complicates assessment of the potential impact of extending the vaccination programme as a poorly matched vaccine would be less effective and therefore yield fewer benefits.

There are limited data on influenza vaccination uptake rates for the target population. Irish data were obtained from the HPSC and relate to the administration of influenza vaccines reimbursed through the HSE's Seasonal Influenza Vaccination Programme. Vaccination coverage is however calculated as a percentage of the total population rather than the eligible population and therefore appears relatively low for this age group.[68] During the 2021-2022 season, the influenza programme was temporarily extended to include all individuals aged 50 to 64 years; despite this, the uptake rate remained low at approximately 27%. It may be the case that there was insufficient awareness of the expanded eligibility or that individuals' behaviours were impacted by the COVID-19 pandemic, resulting in the suboptimal uptake rate observed. As noted in Section 3.4.1, the HPSC data represent an underestimate of total uptake as they exclude, for example, instances where the vaccine is paid for privately. Nevertheless, the likelihood of achieving an increased uptake is an important consideration when contemplating the extension of the influenza vaccination 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.[85] 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.[86-88]

4 Costing analysis

Key points

- A costing analysis was conducted to estimate the potential costs and benefits associated with expanding the HSE's Seasonal Influenza Vaccination Programme to include those aged 50 to 64 years in the general population for the 2023-2024 influenza season. The potential impact on health outcomes and healthcare utilisation of extending vaccination is subject to considerable uncertainty. Aside from the coverage, key parameters include the vaccine effectiveness, likelihood of hospitalisation and ICU admission, and typical length of stay in hospital and ICU. A wide range of projected influenza vaccine uptake rates were assessed to ascertain the potential costs and effects of extending vaccination eligibility.
- Based on figures from the Central Statistics Office, the total population aged 50 to 64 years is estimated to be 914,379.
- Considering HPSC data, which reflect uptake of influenza vaccines reimbursed through the HSE's Seasonal Influenza Vaccination Programme as a percentage of the total population, annual uptake among those aged 50 to 64 years was approximately 28% over the past two influenza seasons.
- The HPSC data underestimate total influenza vaccine uptake as they exclude instances where individuals or employers (as part of an occupational health scheme) pay for the vaccine privately.
- If uptake of the reimbursed vaccine for this cohort increases from 28% (recent uptake) to 35% (which is considered achievable, supported by an appropriate public health information campaign), the mean incremental cost to the HSE of extending eligibility for the 2023-2024 season is estimated at approximately €2.27 million. This comprises €1.52 million in fees for administering the vaccine and €0.75 million for the vaccine (assuming a vaccine cost of €10 plus 23% VAT per dose).
    - Given the uncertainty in vaccine cost, a range of costs were modelled from a low of €5 to a high of €15 per dose. Based on this, vaccine costs could range from €0.38 million (€5 plus 23% VAT per dose) to €1.13 million (€15 plus 23% VAT per dose).
- Given that there appears to be a trend of increasing rates of influenza, and influenza-related hospital discharges, hospital discharges with an ICU visit and

mortality with increased age, a decision could be made to limit the programme extension to one or more of the five-year age band subgroups within this cohort.

    - Under the same assumptions of an uptake increase to 35% and using a vaccine cost of €10 (plus 23% VAT per dose), the estimated total mean incremental cost is approximately €0.68 million if extended just to those aged 60 years and older and €1.43 million if extended just to those aged 55 years and older.

- If vaccine uptake increases from 28% to 35%, it is estimated that a mean of 77 influenza cases, 22 influenza-related hospital discharges and 136 influenza-related bed days could be avoided. The corresponding mean reduction in influenza-related hospital costs for a 35% influenza vaccination uptake rate is estimated at €0.11 million.
- There is considerable uncertainty surrounding the potential to increase uptake of the programme and the potential benefits of extending eligibility. In the absence of disaggregated data, the analysis assumed equal benefit for all vaccine recipients in this age range when in reality, those at increased risk of severe disease are already eligible for a free influenza vaccination.
- As vaccination uptake rates increase, the risk profile of the population may change, so that the additional benefits that accrue may decrease as vaccination rates increase.
- Given the relatively modest absolute number of influenza-related hospitalisations in this age group, and the substantial year-on-year variability in vaccine effectiveness, the potential for a reduction in demand for hospital care is likely to be small.

4.1 Introduction

This chapter outlines the potential cost and effects to the HSE associated with expanding its seasonal influenza vaccinationprogramme in Ireland to include those aged 50 to 64 years in the general population for the 2023-2024 influenza season.

4.2 Methods

For the purpose of this rapid HTA, a costing analysis was conducted. The cost of the vaccine, along with any changes to organisational processes resulting from the inclusion of this subgroup in the seasonal influenza vaccination programme were identified and considered.

4.2.1 Study perspective

In line with national guidelines, costs and benefits were assessed from the perspective of the publicly-funded health and social care system, the Health Service Executive (HSE).[92] As such, only direct medical costs are included. Indirect costs such as decreased productivity associated with morbidity and mortality, or out-of-pocket expenses incurred for patients (for example, travel costs incurred by patients receiving the vaccination) were excluded from the analysis.

4.2.2 Technology

The technology being assessed is an expansion of the HSE's Seasonal Influenza Vaccination Programme in Ireland to include those aged 50 to 64 years in the general population (that is, those not currently included in the programme, for example healthcare workers and those at increased risk of severe disease) for the 2023-2024 flu season. The aim of the intervention is to reduce incidence of influenza amongst this subgroup and thereby reduce the burden of disease on the HSE.

4.2.3 Choice of comparators

One comparator is considered in the costing analysis: the current HSE seasonal influenza vaccination programme, which excludes those aged 50 to 64 years in the general population, with the exception of those in identified risk groups.

4.2.4 Time horizon

The time horizon represents the timeframe over which resource use is planned. For the purpose of this rapid HTA, the potential cost associated with expanding the HSE's Seasonal Influenza Vaccination Programme to include those aged 50 to 64 years in the general population was estimated for the 2023-2024 influenza season.

4.2.5 Measurement and valuation of resources

Estimation of costs was carried out using a range of methods as appropriate to each item.[92] Where possible, these estimates were informed by national data including data from the HSE's Health Protection Surveillance Centre (HPSC) and its Primary Care Reimbursement Service (PCRS). Where limited data were available, these were supplemented by expert opinion from within the HTA team and relevant external stakeholders. Where possible, data from international sources were used to validate assumptions. Specific data used to inform resource use and valuation estimates are described separately for each cost item below.

4.2.6 Epidemiological inputs

Target population

The target population is those aged 50 to 64 years, excluding those who are already eligible for the influenza vaccination, that is, for example, those at increased clinical risk and healthcare workers.[5] There is much uncertainty relating to the number of individuals who are classified as being at increased clinical risk; these data are not routinely collected by the HPSC.

The HSE defines a number of health conditions that put an individual at higher risk of severe disease due to influenza. These include, chronic heart disease, chronic liver disease, chronic kidney failure, chronic respiratory disease and diabetes.[5] The Healthy Ireland Survey 2022,[93] reports that 31% (of those aged 15 years or older) have a long-standing illness or health problem, lasting at least six months or more; this prevalence was 28% in the 2015 report,[94] and in those aged 55 years or older, the prevalence was 48% (2015). Data from The Irish Longitudinal Study of Ageing report that 74% of adults aged 58 years and older report the presence of two or more medical conditions (2018).[95]

The HSE recommends the seasonal influenza vaccination for all healthcare workers.[5] At least 20% of healthcare workers are infected with influenza every year and healthcare workers may spread influenza to patients, family and colleagues.[5] In 2022, the CSO reported that there were over 325,000 people aged between 15 and 89 years employed in health and social care activities;[96] however these data are not disaggregated by age. Disaggregated data are available for some professional groups. For example, nursing and midwifery staff comprise a substantial percentage of those working in health and social care. Data from the Nursing and Midwifery Board of Ireland report that in 2022, 29% of all registered nurses were aged 50 to 64 years (n=23,425).[97]

Given the uncertainty surrounding estimation of the target population (that is, those aged 50 to 64 years and not at increased risk of severe disease), we considered the total population aged 50 to 64 years. Data from the Central Statistics Office (CSO) show that the projected population for those aged 50 to 64 years is 914,379 for 2023.[98]

Vaccine uptake

The costing analysis required historical and projected uptake rates. The historical uptake rate for seasonal influenza vaccination (including healthcare workers and those at increased risk of severe disease) was obtained from the HPSC and is reported in Chapter 3 as approximately 26.5% (n=233,034) of all individuals aged 50 to 64 years for the 2021-2022 influenza season and 30.2% for the 2022-2023 influenza season (n=270,785).[68, 98] These figures reflect the administration of influenza vaccines reimbursed through the HSE's Seasonal Influenza Vaccination Programme across all settings, that is, GP practices, community pharmacies, long

term care facilities and hospitals. Based on the average uptake in those aged 50 to 64 years over the two seasons (2021-2022 and 2022-2023), the current influenza vaccination uptake rate was calculated to be approximately 28%; costs and benefits at higher projected uptake rates were considered relative to this. Of note, the eligibility criteria for these two years differed given the temporary extension during the 2021-2022 influenza season to include those aged 50 to 64 years regardless of their risk status (that is the target population for this rapid HTA).

Data from the UK suggest that influenza vaccination uptake in those aged 50 to 64 years (regardless of their risk status) was 52.5% for the 2021-2022 season[70] and 45.2% for the 2020-2021 season;[99] which corresponded to an uptake rate of 66.1% and 66.3%, respectively in those aged 50 to 64 years at increased risk of severe disease, and 45.7% and 35.2%, respectively for those in this age group but not considered to be at increased risk of severe disease. Given this international evidence of potential uptake, a wide range of projected uptake rates were assessed to ascertain the potential costs and effects of extending vaccination eligibility.

Health outcomes

Data relating to health outcomes are reported in Chapter 3 and were used in the analysis to ascertain the potential reduction in the number of notified cases, number of hospital admissions and associated bed days, number of hospital admissions that include an ICU stay and associated bed days, and the reduction in mortality.

4.2.7 Cost inputs

Vaccine

In Ireland, the influenza vaccine is administered in primary care settings by GP practices and authorised pharmacists. Pharmacists have been designated in law to provide a seasonal influenza vaccination service in pharmacies since 2011. Legislation was amended in 2020 which allowed pharmacists who are appropriately trained to supply and administer the vaccine at any suitable location (that is, not necessarily within the pharmacy premises) with regard to the need to protect the welfare of the public and consideration of public convenience.[100] Supplies of the influenza vaccine required for individuals eligible for the HSE's Seasonal Influenza Vaccination Programme may be ordered by approved GPs and pharmacists through the HSE National Cold Chain Service, with supplies of the vaccine delivered directly to their premises. Pharmacists and GPs are notified prior to the beginning of each influenza season with a list of vaccine brands that are available for ordering; this list is determined annually by the HSE based on a competitive tender competition open to distributors of vaccines authorised for use in Ireland. Reimbursement of GPs and pharmacists for administration of the vaccine is through the HSE's Primary Care Reimbursement Service (PCRS). The schedule of fees is outlined in the PCRS annual

reports. The fee for administering the QIV vaccine is set at €15 for both GPs and pharmacists.[101] They are also eligible for a payment of €100 for every 10 unique patients to whom the QIV vaccine is administered.[101] Based on the number of GP practices and pharmacies in Ireland, and the variability in demand across sites, the average cost of vaccinating an individual is about €24.88 (95% CI: 24.80 to 24.99); this includes administering the vaccine and the additional amount payable for every 10 unique patients vaccinated. 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 confident. To inform decision making, estimates based on a range of costs have been included in the analysis. Table 4.1 reports the cost of vaccinating one individual based on a range of possible vaccine costs.

Table 4.1 Summary of the cost of vaccinating one individual at varying vaccine costs

Vaccine dose cost (€)	Vaccine dose cost with 23% VAT (€)	Administration fee (€)	Total cost of vaccinating one individual (€)
5.00	6.15	24.88	31.03
7.50	9.23	24.88	34.11
10.00	12.30	24.88	37.18
12.50	15.38	24.88	40.26
15.00	18.45	24.88	43.33

Key: VAT – value-added tax.

Public health information campaign

It is assumed that implementation of an expansion of the influenza vaccination programme will be accompanied by a public health information campaign aimed at encouraging uptake of vaccination. It is understood that the current HSE budget for the influenza-related public health information campaign would cover the costs of extending the influenza vaccination programme to the target population. In general, the cost of public health information campaigns is strongly influenced by the approach adopted with consideration given to practical concerns such as how the target population can best be reached.

The individual components that may determine the cost of a public health information campaign may include:

- qualitative research – investigation of the target audience's knowledge, awareness levels, information gaps and or misconceptions
- creative development – campaign development based on the findings from the qualitative research which will vary according to the type of media campaign required (for example, radio and press), and require the involvement of creative agencies and analysis
- focus testing – testing of creative routes (for example, focus groups)

- media plan – the duration of the media campaign.[102]

The use of direct written correspondence (either a letter or postcard) has been shown to increase influenza vaccination uptake by approximately 16%, relative to mass communication alone.[103] Another option would be to create an influenza vaccine registration database similar to the COVID-19 vaccine registration database. From this, people would receive text messages with relevant reminders and updates.[104]

Hospitalisation

The average cost of hospitalisation associated with influenza was estimated using data from the HSE's Healthcare Pricing Office. From 2010 to 2022, 92% of influenza discharges were classified into one of four Diagnosis Related Groups (DRGs). The average cost of an episode over the 13 years was €3,614. However, there has been an upward trend in the average cost of an episode, driven by the increasing cost associated with DRG D63A (Otitis media and upper respiratory infection with major complications), which accounts for almost 70% of influenza-related episodes. Based on trends, it was estimated that a typical influenza-related hospital episode in the 2023/24 season would cost €4,839 (95% confidence interval €3,884 to €5,806).

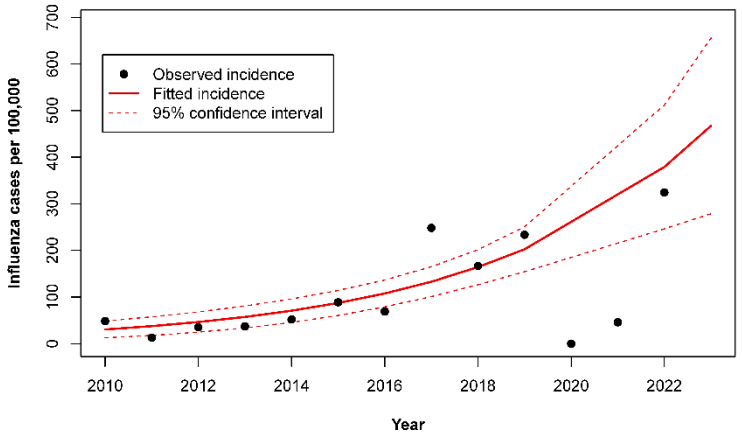
As reported in Chapter 3, the average length of stay in hospital for influenza according to HIPE data is 6.2 days (excluding 2020 and 2021 which were considered to be not representative due to COVID-19). For those who had an ICU admission during their stay, the mean length of stay (including both days spent in ICU and other hospital wards) was 14.4 days (again excluding 2020 and 2021). These figures reflect a period of time when vaccinations were available to, among others, those aged 50 to 64 years and at increased risk of severe disease. Of those that were hospitalised, neither the vaccination status nor the proportion that were in an identified risk category is known. Relative to those identified as being at increased risk, those in the general population (that is, the target population in this rapid HTA) are less likely to be hospitalised and may typically have a shorter length of stay.

4.2.8 Summary of assumptions and handling of uncertainty for costing analysis

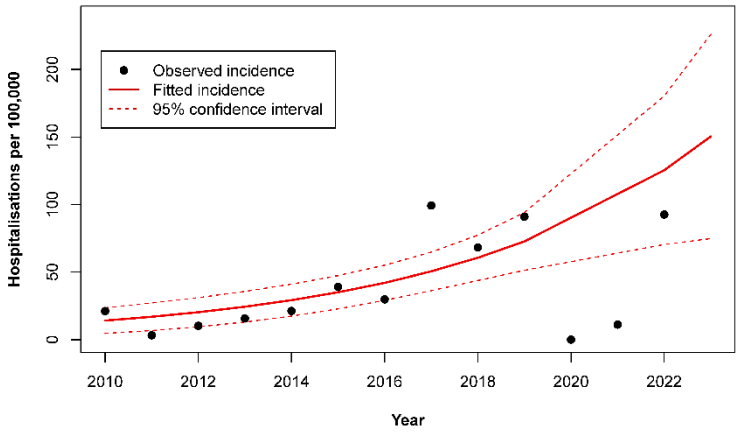
The potential impact on health outcomes and healthcare utilisation of extending vaccination is subject to considerable uncertainty. Aside from the coverage, key parameters include the vaccine effectiveness, the likelihood of hospitalisation and ICU admission, and the typical length of stay in hospital and ICU. While these parameters are subject to variability across patients, the analysis here focused on year-on-year fluctuations. HSE data indicate evidence of a trend for increasing incidence of notified influenza cases from 2010 to 2022 in 50 to 64 year olds, and corresponding increases in hospital and ICU admission, and mortality (Figure 4.1).

Figure 4.1 Changes in incidence over time

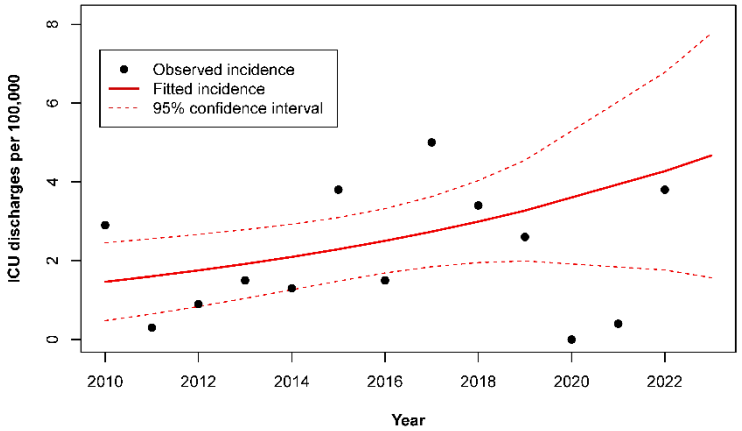
a) Notified influenza cases



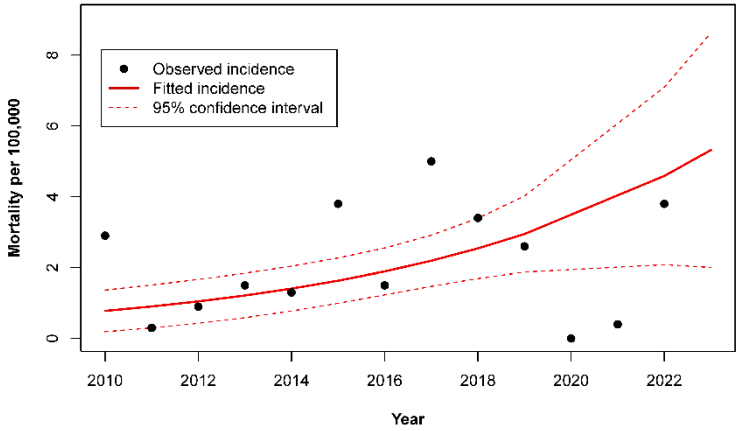
b) Hospital discharge



c) Intensive care unit discharge



d) Mortality



The data for the years 2020 and 2021 are clearly influenced by the COVID-19 pandemic, and hence are a poor representation of past and future incidence. The incidence for 2023 was estimated using a generalised linear model excluding the 2020 and 2021 data. In addition to incidence, uncertainty around hospital and ICU length of stay was estimated using bootstrapping of historical data. There was no evidence of a temporal trend in length of stay; years with unusually high mean length of stay values were associated with small numbers of patients, potentially being skewed by one or a small number of outliers. Vaccine effectiveness was varied, with the mean and range based on a UK modelling study using data from the 2018 to 2019 influenza season.[105]

The vaccine effectiveness, incidence and length of stay parameters were all varied within plausible ranges and the potential impact on incidence and bed days was estimated. Table 4.2 provides a summary of the parameter values used in the sensitivity analysis.

Table 4.2 Parameter values used in the sensitivity analysis

Parameter	Mean	(95% CI)
Current vaccine uptake (%)	28.4%	(26.5% to 30.2%)
Vaccine effectiveness (%)	32%	(12% to 52%)
Influenza incidence (per 100,000)	466.5	(291.9 to 686.7)
Hospitalised (per 100,000)	150.7	(81.7 to 242.3)
ICU discharge (per 100,000)	4.7	(1.9 to 8.7)
Mortality (per 100,000)	5.3	(2.5 to 9.2)
Hospital length of stay (days)	6.2	(5.8 to 6.7)
Hospital length of stay that includes an ICU stay (days)	14.4	(12.7 to 16.1)
Cost of hospital episode	€4,839	(€3,884 to €5,806)

Key: ICU – intensive care unit.

In the main analysis, vaccine effectiveness was allowed to vary around its mean. In reality, the vaccine effectiveness is likely to be associated with matching to strain, and hence it may be high in some years and low in others, with the mean reflecting the long-run average rather than the experience in any single year. To acknowledge that the distribution may be bimodal, a scenario analysis was carried out in which the vaccine effectiveness was set at high value of 57% while all other parameters were set at their means. A worst case scenario would be for the vaccine to have no effect and therefore be associated with no reduction in cases of influenza.

4.3 Results

4.3.1 Potential costs associated with expanding the influenza vaccination programme

Table 4.3 presents the potential incremental costs (at varying influenza vaccination uptake rates and varying vaccine costs) to the HSE associated with expanding access to those aged 50 to 64 years regardless of risk status. These estimates use a projected population of 914,379 for those aged 50 to 64 years and assume approximately 28% of this population are already availing of the influenza vaccine through the HSE's Seasonal Influenza Vaccination Programme.

If vaccine uptake for this cohort increases from 28% (recent uptake) to 35%, the total mean incremental cost of extending eligibility for the 2023-2024 season is estimated at €2,267,442. This comprises €1,517,320 in fees for administering the vaccine and €750,122 for the vaccine (assuming a unit cost of €10 plus 23% VAT). At this uptake, considering the range of unit costs modelled, incremental vaccine costs could range from €375,061 (€5 plus 23% VAT per dose) to €1,125,183 (€15 plus 23% VAT per dose). See Table 4.3 for the incremental vaccination costs associated with varying influenza vaccination uptake rates.

Table 4.3 Mean incremental vaccination costs associated with varying influenza vaccination uptake rates in those aged 50 to 64 years (in millions)

Uptake %	Incremental costs of vaccination at various uptake rates and vaccine costs (95%CI) (€ in millions)					
	Administration fee	Vaccine cost (€5.00 plus 23% VAT)	Vaccine cost (€7.50 plus 23% VAT)	Vaccine cost (€10.00 plus 23% VAT)	Vaccine cost (€12.50 plus 23% VAT)	Vaccine cost (€15.00 plus 23% VAT)
28	0	0	0	0	0	0
32	0.83 (0.42 to 1.24)	0.21 (0.10 to 0.31)	0.31 (0.16 to 0.46)	0.41 (0.21 to 0.62)	0.52 (0.26 to 0.77)	0.62 (0.31 to 0.92)
33	1.06 (0.65 to 1.47)	0.26 (0.16 to 0.36)	0.39 (0.24 to 0.55)	0.52 (0.32 to 0.73)	0.66 (0.40 to 0.91)	0.79 (0.48 to 1.09)
34	1.29 (0.87 to 1.70)	0.32 (0.22 to 0.42)	0.48 (0.32 to 0.63)	0.64 (0.43 to 0.84)	0.80 (0.54 to 1.05)	0.96 (0.65 to 1.26)
35	**1.52 (1.10 to 1.93)**	**0.38 (0.27 to 0.48)**	**0.56 (0.41 to 0.71)**	**0.75 (0.54 to 0.95)**	**0.94 (0.68 to 1.19)**	**1.13 (0.82 to 1.43)**
36	1.74 (1.33 to 2.15)	0.43 (0.33 to 0.53)	0.65 (0.49 to 0.80)	0.86 (0.66 to 1.06)	1.08 (0.82 to 1.33)	1.29 (0.99 to 1.60)
37	1.97 (1.56 to 2.34)	0.49 (0.38 to 0.59)	0.73 (0.58 to 0.88)	0.98 (0.77 to 1.18)	1.22 (0.96 to 1.47)	1.46 (1.15 to 1.77)
38	2.20 (1.78 to 2.61)	0.54 (0.44 to 0.65)	0.82 (0.66 to 0.97)	1.09 (0.88 to 1.29)	1.36 (1.10 to 1.61)	1.63 (1.32 to 1.94)
39	2.43 (2.01 to 2.84)	0.60 (0.50 to 0.70)	0.90 (0.75 to 1.05)	1.20 (1.00 to 1.40)	1.50 (1.24 to 1.75)	1.80 (1.49 to 2.10)
40	2.65 (2.24 to 3.06)	0.66 (0.55 to 0.76)	0.98 (0.83 to 1.14)	1.31 (1.11 to 1.52)	1.64 (1.38 to 1.89)	1.97 (1.66 to 2.27)
41	2.88 (2.47 to 3.29)	0.71 (0.61 to 0.81)	1.07 (0.91 to 1.22)	1.42 (1.22 to 1.63)	1.78 (1.52 to 2.03)	2.14 (1.83 to 2.44)
42	3.11 (2.69 to 3.52)	0.77 (0.67 to 0.87)	1.15 (1.00 to 1.31)	1.54 (1.33 to 1.74)	1.92 (1.67 to 2.18)	2.31 (1.20 to 2.61)
43	3.34 (2.92 to 3.75)	0.82 (0.72 to 0.93)	1.24 (1.08 to 1.39)	1.65 (1.44 to 1.85)	2.06 (1.81 to 2.32)	2.47 (2.17 to 2.78)
44	3.56 (3.15 to 3.97)	0.88 (0.78 to 0.98)	1.32 (1.17 to 1.47)	1.76 (1.56 to 1.96)	2.20 (1.95 to 2.46)	2.64 (2.34 to 2.95)
45	3.79 (3.38 to 4.20)	0.94 (0.83 to 1.04)	1.41 (1.23 to 1.56)	1.87 (1.67 to 2.08)	2.34 (2.09 to 2.60)	2.81 (2.50 to 3.12)
50	4.93 (4.51 to 5.34)	1.22 (1.12 to 1.32)	1.83 (1.67 to 1.98)	2.44 (2.23 to 2.64)	3.05 (2.79 to 3.30)	3.66 (3.35 to 3.60)
55	6.07(5.65 to 6.48)	1.50 (1.40 to 1.60)	2.25 (2.10 to 2.40)	3.00 (2.79 to 3.20)	3.75 (3.49 to 4.00)	4.50 (4.19 to 4.80)
60	7.20 (6.79 to 7.61)	1.78 (1.68 to 1.90)	2.67 (2.52 to 2.82)	3.56 (3.36 to 3.76)	4.45 (4.20 to 4.71)	5.34 (5.03 to 5.65)
65	8.34 (7.93 to 8.75)	2.06 (1.96 to 2.16)	3.09 (2.94 to 3.24)	4.12 (3.92 to 4.33)	5.16 (4.90 to 5.41)	6.19 (5.88 to 6.49)
70	9.48 (9.06 to 9.89)	2.34 (2.24 to 2.44)	3.51 (3.36 to 3.67)	4.69 (4.48 to 4.89)	5.86 (5.60 to 6.11)	7.029 (6.72 to 7.33)

Note: Uptake reflects total uptake in those aged 50 to 64 years old, including uptake in those in identified risk categories and those in the general population.
Key: CI – confidence intervals; VAT – value-added tax.

As reported in Chapter 3, there appears to be a trend of increasing rates of notified influenza cases, hospital admissions, ICU admissions and mortality with increased age. While there are differences in the rates of influenza cases and outcomes across the three age bands, it is unclear whether the differences observed would result in substantial benefits for one subgroup over another. As such, Table 4.4 shows the incremental cost of vaccination (assuming a vaccine cost of €10 plus 23% VAT and including the administration fees) by five-year age band for a range of uptake values. The confidence intervals reflect the uncertainty in the uptake based on current eligibility rules. If the vaccination uptake rate increased from 28% (recent uptake in this cohort) to 35%, the estimated total mean incremental cost would be €676,085 if extended to those aged 60 years and older and €1,427,124 if extended to those aged 55 years and older.

Table 4.4 Mean incremental vaccination costs associated with varying influenza vaccination uptake rates in those aged 50 to 64 years (in millions)

Uptake %	Mean incremental vaccination cost (95%CI) (€ in millions)		
	50 to 54 years	55 to 59 years	60 to 64 years
28	0	0	0
32	0.45 (0.24 to 0.68)	0.41 (0.22 to 0.62)	0.37 (0.19 to 0.55)
33	0.58 (0.36 to 0.80)	0.52 (0.33 to 0.73)	0.47 (0.30 to 0.66)
34	0.70 (0.49 to 0.93)	0.64 (0.44 to 0.84)	0.57 (0.40 to 0.76)
35	**0.83 (0.61 to 1.05)**	**0.75 (0.56 to 0.96)**	**0.68 (0.50 to 0.86)**
36	0.95 (0.74 to 1.18)	0.86 (0.67 to 1.07)	0.78 (0.60 to 0.96)
37	1.07 (0.86 to 1.30)	0.98 (0.78 to 1.18)	0.88 (0.70 to 1.06)
38	1.20 (0.99 to 1.43)	1.09 (0.90 to 1.30)	0.98 (0.81 to 1.17)
39	1.32 (1.11 to 1.55)	1.20 (1.01 to 1.41)	1.08 (0.91 to 1.27)
40	1.45 (1.23 to 1.67)	1.32 (1.12 to 1.52)	1.19 (1.01 to 1.37)
41	1.57 (1.36 to 1.80)	1.43 (1.24 to 1.64)	1.29 (1.11 to 1.47)
42	1.70 (1.48 to 1.92)	1.54 (1.35 to 1.75)	1.39 (1.22 to 1.58)
43	1.82 (1.61 to 2.05)	1.66 (1.46 to 1.86)	1.49 (1.32 to 1.68)
44	1.95 (1.73 to 2.17)	1.77 (1.58 to 1.98)	1.59 (1.42 to 1.78)
45	2.07 (1.86 to 2.30)	1.88 (1.69 to 2.09)	1.70 (1.52 to 1.89)
50	2.69 (2.48 to 2.92)	2.45 (2.26 to 2.66)	2.21 (2.03 to 2.39)
55	3.32 (3.10 to 3.54)	3.02 (2.82 to 3.22)	2.72 (2.54 to 2.90)
60	3.94 (3.73 to 4.17)	3.58 (3.39 to 3.79)	3.23 (3.05 to 3.41)
65	4.60 (4.35 to 4.79)	4.15 (3.96 to 4.36)	3.74 (3.56 to 3.92)
70	5.19 (4.97 to 5.41)	4.72 (4.52 to 4.92)	4.25 (4.07 to 4.43)

Note: Uptake reflects total uptake in those aged 50 to 64 years old, including uptake in those in identified risk categories and those in the general population.
Estimated incremental costs comprise the cost of administering the vaccine and assume a vaccine unit cost of €10.00 plus 23% VAT
Key: CI – confidence intervals; VAT – value-added tax.

4.3.2 Potential benefits as a result of expanding the influenza vaccination programme

Table 4.5 provides a summary of influenza outcomes that could be avoided in those aged 50 to 64 years at varying influenza vaccination uptake rates for the 2023-2024 influenza season. On average, it is estimated that an increase in vaccine uptake from 28% to 35% would result in the avoidance of 77 influenza cases, 22 influenza-related hospital discharges, one influenza-related hospital discharge that includes an ICU stay, and one death.

Table 4.5 Summary of influenza outcomes that could be avoided at varying influenza vaccination uptake rates

Projected influenza vaccination uptake rate (%)	Mean number of notified influenza cases avoided (n)	Mean number of influenza-related hospital discharges avoided (n)	Mean number of influenza-related hospital discharges which include an intensive care unit stay avoided (n)	Mean number of influenza-related deaths avoided (n)
28	0.0	0.0	0.0	0.0
32	42.2	12.0	0.5	0.5
33	53.6	15.3	0.6	0.6
34	65.1	18.5	0.8	0.8
35	**76.6**	**21.8**	**0.9**	**0.9**
36	88.0	25.1	1.1	1.0
37	99.5	28.3	1.2	1.2
38	110.9	31.6	1.3	1.3
39	122.4	34.8	1.5	1.5
40	133.9	38.1	1.6	1.6
41	145.3	41.3	1.7	1.7
42	156.8	44.6	1.9	1.9
43	168.2	47.9	2.0	2.0
44	179.7	51.1	2.1	2.1
45	191.1	54.4	2.3	2.3
50	248.4	70.7	3.0	3.0
55	305.7	86.9	3.6	3.6
60	363.0	103.2	4.3	4.3
65	420.3	119.5	5.0	5.0
70	477.6	135.8	5.7	5.7

Note: Modelled data reflect the total population aged 50 to 64 years including those at higher risk of severe disease who are already eligible for vaccination as part of the HSE's Seasonal Influenza Vaccination Programme.

There is considerable uncertainty surrounding these estimates, especially as those most likely to experience severe disease, and consequently, be hospitalised with or die from influenza-related complications, are already eligible for vaccination. Perception of risk and motivation for vaccination may differ for this cohort, so that when total vaccination uptake rates are low, individuals at elevated risk of severe disease are likely to comprise a higher proportion of those vaccinated. As vaccination uptake rates increase, the risk profile of the population may change. To this end, the upper and lower bounds of the point estimates are reported in Figures 4.2 to 4.5.

Figure 4.2 Mean number of notified influenza cases avoided at varying influenza vaccination uptake rates

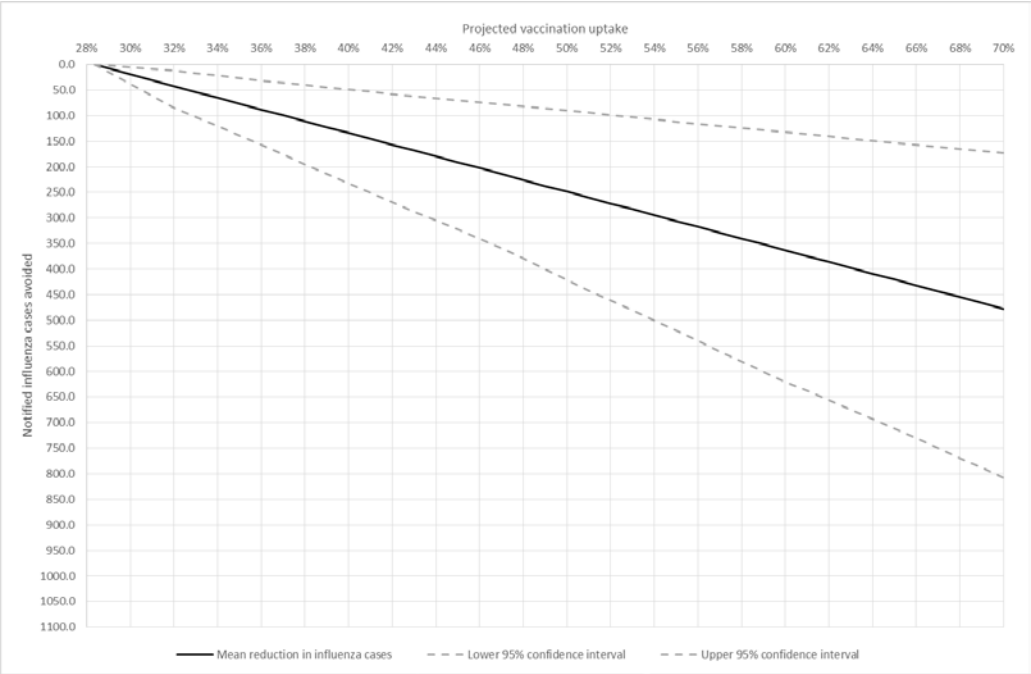


Figure 4.3 Mean number of influenza-related hospital discharges avoided at varying influenza vaccination uptake rates

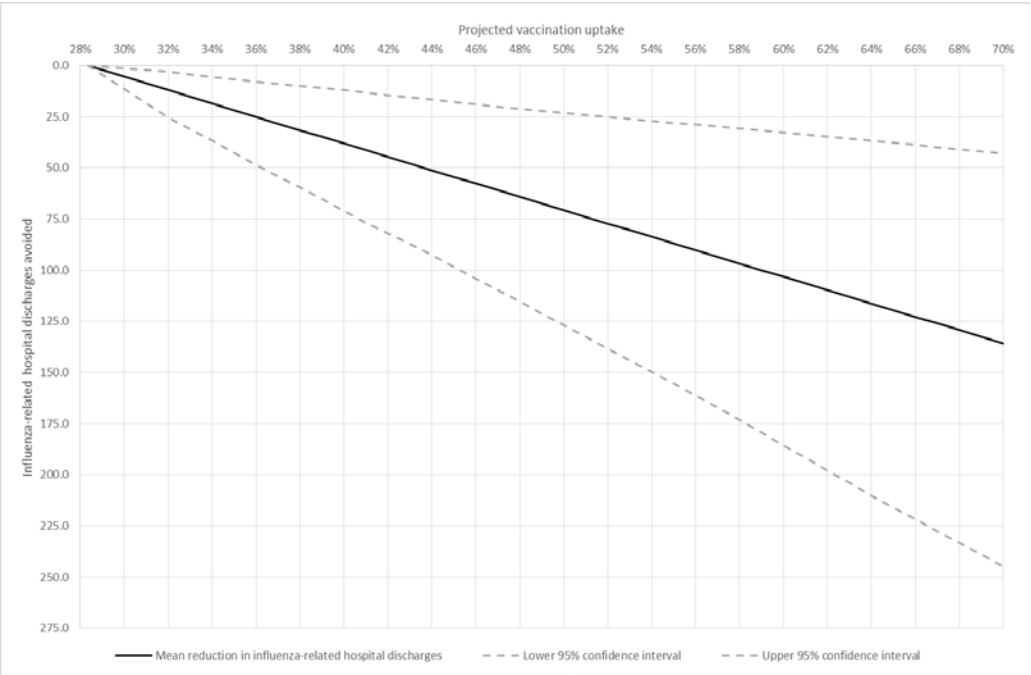


Figure 4.4 Mean number of influenza-related hospital discharges that include an intensive care unit stay avoided at varying influenza vaccination uptake rates

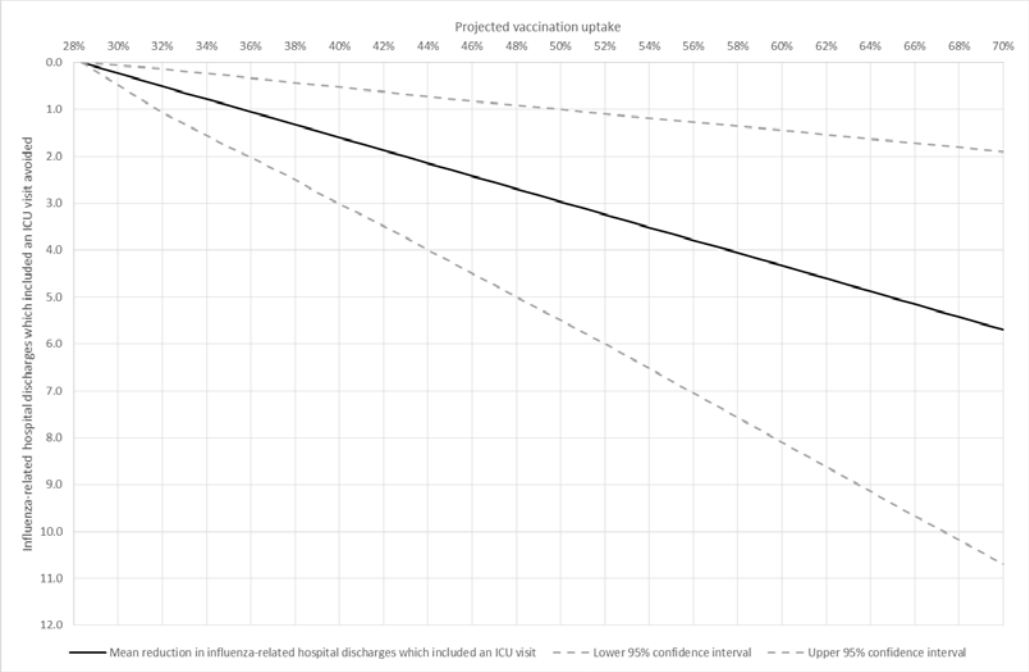


Figure 4.5 Mean number of influenza-related deaths avoided at varying influenza vaccination uptake rates

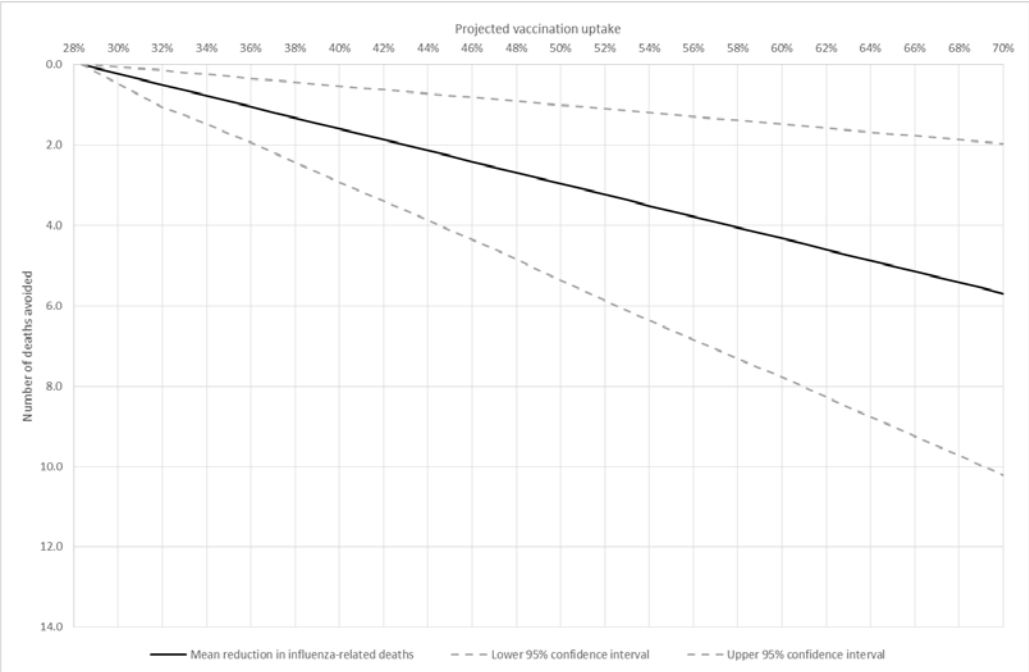


Table 4.6 provides an overview of the mean annual number of influenza-related hospital bed days, influenza-related hospital bed days that include an ICU stay and influenza-related hospital costs avoided at varying influenza vaccine uptake rates. On

average, it is estimated that an increase in vaccine uptake from 28% to 35% in those aged 50 to 64 years for 2023-2024 would result in avoidance of 136 influenza-related bed days, 13 bed days associated with influenza-related discharges that includes an ICU stay, and €105,483 in influenza-related hospital costs.

Table 4.6 Summary of bed days and hospital costs that could be avoided at varying influenza vaccination uptake rates

Projected influenza vaccination uptake rate (%)	Mean influenza-related hospital bed days avoided (n)	Mean influenza-related hospital bed days which included an intensive care unit stay avoided (n)	Mean influenza-related hospital costs avoided (€)
28	0.0	0.0	0
32	75.0	7.2	58,203
33	95.3	9.2	73,963
34	115.6	11.2	89,723
35	**135.8**	**13.1**	**105,483**
36	156.1	15.1	121,243
37	176.4	17.1	137,002
38	196.7	19.0	152,762
39	217.0	21.0	168,522
40	237.3	22.9	184,282
41	257.6	24.9	200,042
42	277.9	26.9	215,801
43	298.1	28.8	231,561
44	318.4	30.8	247,321
45	338.7	32.7	263,081
50	440.1	42.5	341,880
55	541.6	52.4	420,679
60	643.0	62.2	499,478
65	744.4	72.0	578,277
70	845.9	81.8	657,076

Note: Modelled data reflect total population aged 50 to 64 years including those at higher risk of severe disease who are already eligible for vaccination as part of the HSE's Seasonal Influenza Vaccination Programme.

As noted above, the risk of influenza-related complications is not uniform in the population with the likelihood also that those at elevated risk of severe disease will comprise a higher proportion of those vaccinated when vaccination rates are low. These individuals are already eligible for vaccination as part of the HSE's Seasonal Influenza Vaccination Programme. The benefits observed with increasing uptake, in reality, may be much lower than those reported here. To this end, the upper and lower bounds of the point estimates are reported in Figures 4.6 to 4.8, highlighting the considerable uncertainty surrounding these estimates.

Figure 4.6 Mean number of influenza-related hospital bed days avoided at varying influenza vaccination uptake rates

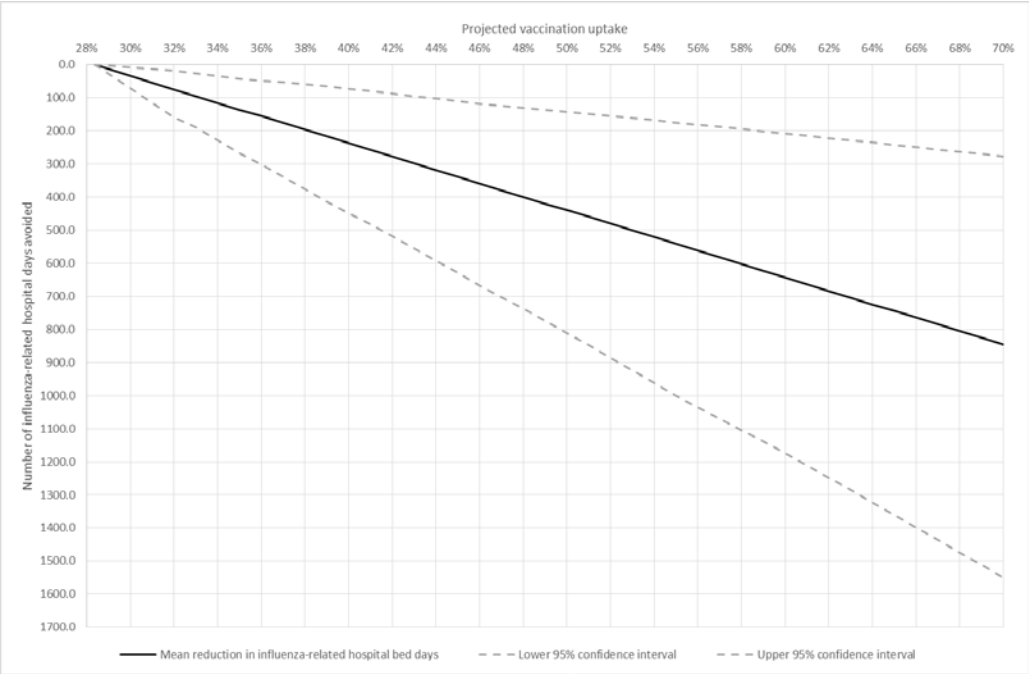


Figure 4.7 Mean number of bed days associated with influenza-related hospital discharges that include an intensive care unit stay avoided at varying influenza vaccination uptake rates

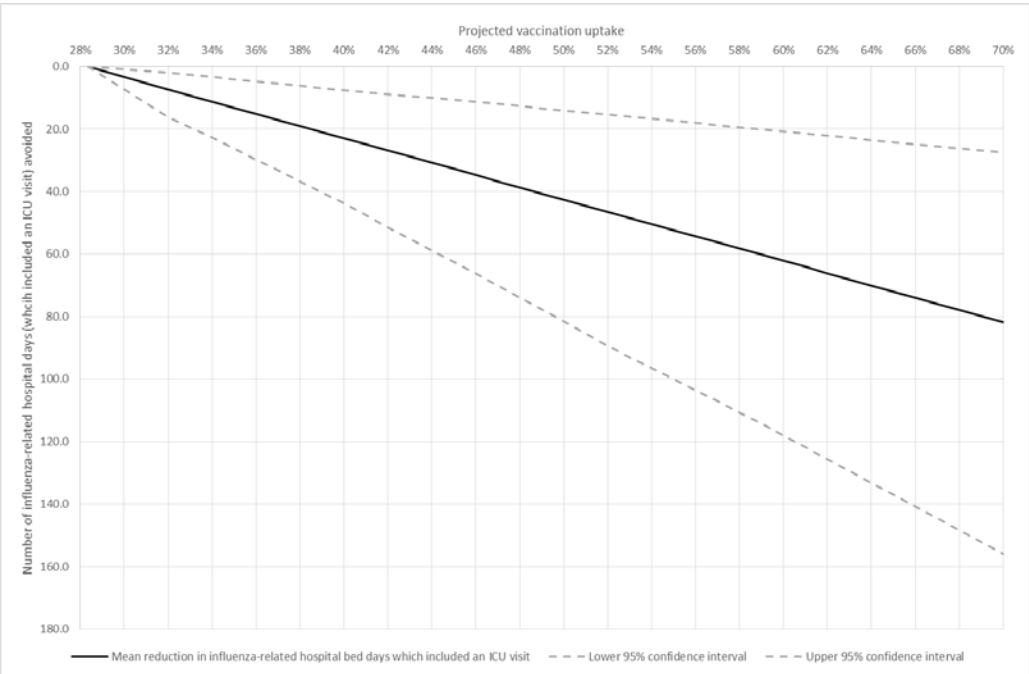
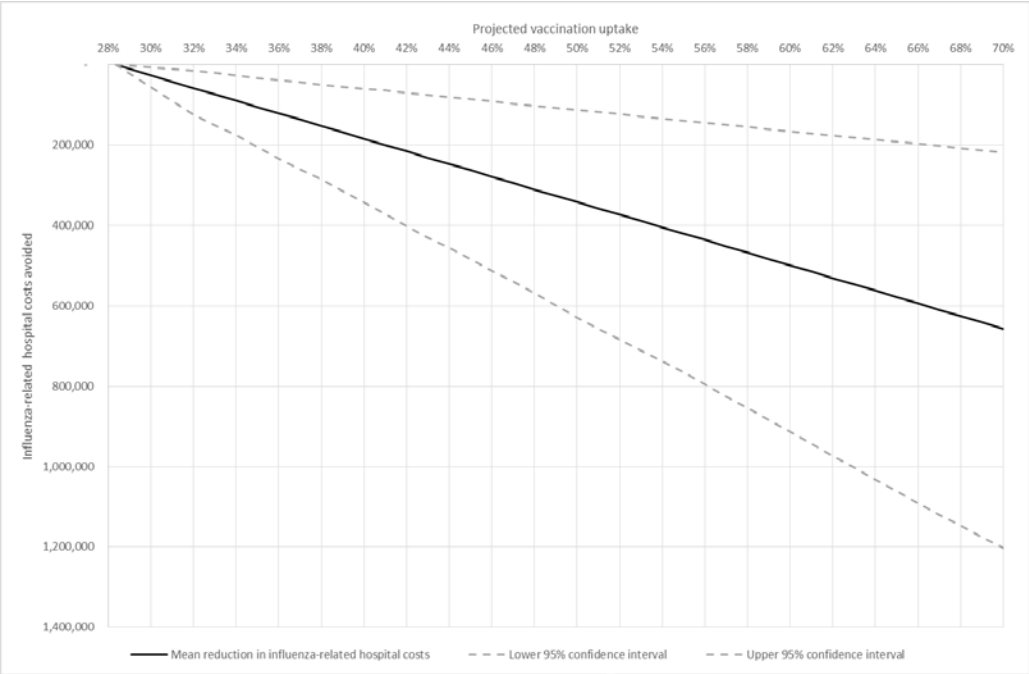


Figure 4.8 Mean reduction in influenza-related hospital costs at varying influenza vaccination uptake rates



4.4 Discussion

A free influenza vaccination is already available to individuals aged 50 to 64 years from a number of specified groups including healthcare workers, residents of nursing homes or other long-term care facilities and those at increased risk of severe disease.[5] The aim of this costing analysis was to estimate the potential costs and benefits associated with extending the HSE's Seasonal Influenza Vaccination Programme for the 2023-2024 influenza season, to include those aged 50 to 64 years who do not fall into one of these categories. In the absence of national data by risk category, vaccination uptake data were reported for the total population aged 50 to 64 years. As such, it was difficult to estimate the potential increase in the target population should the vaccination programme be extended to those not at increased risk of severe disease. Therefore, potential costs and benefits were calculated for the total population aged 50 to 64 years, regardless of their risk status.

The total eligible population aged 50 to 64 years for 2023 was estimated to be 914,379. If vaccine uptake for this cohort increases from 28% (recent uptake) to 35%, the mean incremental cost of extending eligibility for the 2023-2024 season is estimated at approximately €2.27 million. This comprises €1.52 million in fees for administering the vaccine and €0.75 million for the vaccine (assuming a vaccine cost of €10 plus 23% VAT per dose). Given the uncertainty in vaccine ingredient cost, a range of costs were modelled from a low of €5 to a high of €15 per dose. Based on

this, vaccine ingredient costs could range from €0.38 million (€5 plus 23% VAT per dose) to €1.13 million (€15 plus 23% VAT per dose). Given that there appears to be a trend of increasing rates of influenza, hospital discharges, hospital discharges which included an ICU stay and mortality with increased age, a decision could be made to limit the programme extension to subgroups within this cohort. Under the same assumptions of an uptake increase to 35% and a vaccine ingredient cost of €10 (plus 23% VAT), the estimated total mean incremental cost is approximately €0.68 million if extended to those aged 60 years and older and €1.43 million if extended to those aged 55 years and older; these estimates also include the fees for administering the vaccine.

Data from the UK report that (for the 2021-2022 season) the rate of influenza vaccination uptake in those aged 50 to 64 years (regardless of their risk status) was 52.5%.[(99)] Given that this uptake rate is considerably higher than that currently observed in Ireland for this population, outcomes were reported for projected uptake rates ranging from 32% to 70% and a conservative rate of 35% was described in the report. At a projected vaccine uptake rate of 35%, it was assumed that those already availing of influenza vaccination in the 50 to 64 age group would continue to avail of it for the 2023-2024 influenza season.

On average, it is estimated that an increase in vaccine uptake from 28% to 35% in those aged 50 to 64 years for 2023-2024 would result in avoidance of 77 influenza cases, 22 influenza-related hospital discharges, 136 influenza-related bed days and €0.11 million in influenza-related hospital cost. However, there is substantial variability year on year in terms of influenza vaccine effectiveness. This is due to 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. As such, there is much uncertainty around the potential benefits estimated. This issue is discussed further below.

This analysis has a number of limitations. First, costs and benefits were assessed from the perspective of the publicly-funded health and social care system, the HSE. Indirect costs and benefits relating to productivity were also not considered, nor were out-of-pocket expenses incurred for patients included. However, given that eligible individuals can access influenza vaccination locally through their GP or community pharmacy, out-of-pocket costs are likely to be low.

As noted in Section 3.4.1, the reported uptake data are an underestimate of total uptake as they exclude uptake outside the HSE's Seasonal Influenza Vaccination Programme, for example, where individuals or an employer (as part of an occupational health scheme) pay for the vaccine privately. As such, data may reflect influenza-related outcomes where the percentage vaccinated is higher than the estimated 28%. If the HSE programme is extended to include all those aged 50 to

64 years, those obtaining the vaccine privately may choose to receive it as part of the HSE Seasonal Influenza Vaccination Programme increasing programme uptake beyond the 35% modelled. However, this apparent increase in uptake may not result in improved outcomes, but simply reflect a transfer of costs to the HSE if it results in a corresponding reduction in private uptake. While acknowledging this potential, it is noted that expansion of the HSE programme to all those aged 50 to 64 years is unlikely to result in changes to employer practice around providing vaccination to employees; therefore individuals within the target group who currently access free influenza vaccination through an employment-based occupational health scheme, will likely continue to access the vaccine through such schemes.

The projected uptake rate of 35% was an estimate based on historical uptake rates in Ireland and UK uptake rates for the same population group. However, an uptake rate of 35% is higher than historical uptake rates in Ireland. For example, in the 2021-2022 season, the HSE Seasonal Influenza Vaccination Programme was extended to include the target population for this analysis, but uptake rate was approximately 27% for that season. Therefore, the projected uptake rate is open to a lot of uncertainty and if influenza vaccine doses were purchased to fulfill this projected uptake rate, it could result in notable wastage if a lower uptake rate was achieved.

Additionally, vaccination uptake data lacked the specific information required for this analysis. For example, these data were not disaggregated according to those availing of the vaccine due to their increased risk of severe disease. The HSE information system CoVax has been updated to capture influenza vaccination records as well as COVID-19 vaccinations. The aim of the CoVax database is to collate data relating to the administration of influenza and COVID-19 vaccines, regardless of the setting in which they were administered. 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 GPVax portal and include only those vaccinations reimbursed by the HSE. Therefore, while providing an additional useful future source of data in relation to the status of individuals obtaining influenza vaccine, the CoVax data will not be nationally representative.

Influenza outcomes (that is, number of notified cases, hospital admissions, length of stay and mortality) were not disaggregated according to the risk classification of the individual (identified increased risk of severe disease versus general population with

no identified risk). International data highlight the disproportionate burden in those at higher risk of severe disease. Canadian data over seven influenza seasons (2010-2011 to 2016-2017) indicated that in adults aged 50 to 64 years, over 80% of those with an influenza-related hospital admission had an underlying condition associated with a high risk of influenza complications; this compared with 40% of individuals with such conditions in the overall population. Influenza-related hospitalisations and mortality rates were approximately six-fold higher in those with compared to those without underlying conditions.[106] Perception of risk and motivation for vaccination may differ for those at elevated risk, so that when total vaccination uptake rates are low, individuals at elevated risk of severe disease are likely to comprise a higher proportion of those vaccinated. As vaccination uptake rates increase, the risk profile of the population may change, so that the additional benefits that accrue may decrease as vaccination rates increase. Routine collection of information regarding an individual's decision to avail of the vaccine (for example, being a healthcare worker or carer, or being at increased risk of severe disease) would inform future analyses relating to the extension of vaccination programmes. Another limitation is 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 from one influenza season to the next. Finally, the number of influenza-related hospitalisations in this age group is relatively small. As such, there is considerable variability in hospital costs and length of stay from year to year. Some of this variability may be related to the strain of influenza in circulation that season and the degree of vaccine matching.

5 Discussion

As a temporary measure for the 2021-2022 season, given the widespread circulation of SARS-CoV-2 in the community at that time, reimbursement of influenza vaccination for all aged 50 to 64 years (regardless of their risk status) was authorised by the Minister for Health to minimise the overall burden associated with viral respiratory infections. To inform a decision as to whether this group should be included again as a temporary measure for the 2023-2024 season, the Department of Health requested that HIQA complete a rapid health technology assessment (HTA) on the inclusion of the 50 to 64 year age group in the HSE's Seasonal Influenza Vaccination Programme.

5.1 Findings of the rapid health technology 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.

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. In Ireland, anyone can pay for an annual influenza vaccination. However, several population groups (for example, those aged 65 years or older, healthcare workers, those with certain medical conditions, pregnant women and carers) are eligible (and encouraged) to receive a free annual influenza vaccination through the HSE's Seasonal Influenza Vaccination Programme.

There are various types of influenza vaccines, for example, live attenuated influenza vaccine (which are indicated for use in children only), trivalent inactivated influenza vaccines (TIV), which contain three strains of influenza virus, and quadrivalent inactivated influenza vaccines (QIV), also referred to as standard QIVs, which contain four strains of influenza virus. There are also newer and enhanced QIVs which have been developed to improve vaccine effectiveness.

In Ireland, guidance from the National Immunisation Advisory Committee (NIAC) recommends a standard QIV for those aged 50 to 64 years. However, this age group is not routinely included as an at-risk group for whom vaccination is reimbursed by the HSE. As noted above, as a temporary measure for the 2021-2022 season, reimbursement of vaccination for this age group was authorised by the Minister for

Health, to minimise the overall burden associated with viral respiratory infections given the widespread circulation of SARS-CoV-2 in the community at that time. The purpose of this HTA is to inform the inclusion of the general population aged 50 to 64 years in the national seasonal influenza vaccination programme for the 2023 to 2024 season.

A review of current influenza vaccination policy in the EU/EEA and UK was undertaken, which identified differences in vaccine policy with respect to both the age group for which the vaccine is reimbursed and the choice of vaccine. No country reimburses influenza vaccination for the entire target population (those in aged 50 to 64 years and not at increased risk of severe disease) as part of their national immunisation programme. Five EU/EEA countries limit reimbursement to those aged 60 years and older, while two others reimburse vaccination from age 59 years and from age 55 years. These seven countries also differ in the vaccine reimbursed with six of the seven reimbursing standard TID or QIV vaccines while one country reimburses high-dose QIVs. The UK previously included those in the general population aged between 50 and 64 years in their influenza vaccination programme as a temporary measure for the 2020-2021, 2021-2022 and 2022-2023 influenza seasons. However, on 25 May 2023 they reversed this decision for the 2023-2024 influenza season.[38] 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 extend the influenza vaccination programme should be based on Irish data.

Data relating to influenza-like illness (ILI) and influenza were sourced from HIPE and the HPSC. It is acknowledged that influenza represents a subset of ILI. However, consideration of ILI rates provides an indication of the overall burden on the healthcare system, particularly in primary care. Due to insufficient sample sizes for the target population, it was not possible to report the rates of ILI in those aged 50 to 64 years. For the most recent season (2022-2023 season), for which data are still incomplete, the peak ILI consultation rate across all ages was 116.2 per 100,000. According to data from the HPSC for the most recent season (2022-2023), the notified influenza case rate for those aged 50 to 64 years was 256.9 per 100,000 (n=2,078). It is acknowledged that this is an underestimation of the total burden as a proportion of those with influenza will not undergo testing and be formally identified as a case. Again, for the 2022-2023 season, in those with laboratory-confirmed influenza, the hospital admission rate was 67.3 per 100,000 (n=544), the hospital admission rate with an ICU stay was 5.3 per 100,000 (n=43) and the mortality rate was 2.1 per 100,000 (n=17). However, it is important to note that these data relate to the total population aged 50 to 64 years, and therefore include those groups such as healthcare workers and those identified as being at risk of severe disease for whom the vaccine is already reimbursed. It is also noteworthy

that HIPE data (2010 to 2022) indicate substantial year-on-year variability. For example, in those with a primary diagnosis of influenza, there was a mean of 1,244 bed days per annum, but total annual bed days fluctuated between 53 in 2012 to 3,084 in 2018. Similarly, for discharges that included an ICU stay, the mean bed days was 314 days per annum, but this fluctuated between 77 in 2017 to 619 in 2011. During the seasons of peak COVID-19 incidence (2020-2021 and 2021-2022), there was very low incidence of influenza, although incomplete data for 2022-2023 suggest that incidence is returning to pre-pandemic patterns.

Across the three age bands considered in the analysis (50 to 54 years, 55 to 59 years, 60 to 64 years), HPSC (2022-2023 influenza season), and HIPE (2022) data indicate that the total rates of notified cases, hospital admissions with or without an ICU stay and deaths were highest in those aged 60 to 64 years old. When considering incidence, it should be noted that sentinel practice data are based on approximately 5.7% of the population, which equates to approximately 50,000 people aged 50 to 64 years and about 15,000 to 20,000 people in each of the three five-year age band subgroups. As such, the estimates are based on small numbers of cases within the sample and therefore are subject to uncertainty. In terms of outcome data, as noted above, these data relate to the total population aged 50 to 64 years, including those at elevated risk of severe disease who have consistently been eligible for free vaccination. It is not known what proportion of the observed morbidity and mortality occurred in those who were vaccinated or if the proportion of individuals at elevated risk of severe disease differed by age band. Therefore, it is not possible to state that one subgroup within the age range would have a markedly greater benefit from vaccination over another.

There appears to be a trend for increasing incidence of notified influenza from 2010 to 2022 in 50 to 64 year olds, and corresponding increases in hospital and ICU admission, and mortality. However, it is unclear whether the trend for increasing incidence is solely due to increasing cases or if it is also influenced by increased notification. 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 subsequently increased notification of cases, hospitalised cases and hospitalised cases that included an ICU stay 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 (increased use of multiplex polymerase chain reaction testing) and changes to health seeking and testing behaviour during the 2022-2023 season, should also be considered when comparing current influenza rates to previous seasons.

Regarding influenza vaccination uptake rates in those aged 50 to 64 years, the HPSC report an uptake rate of approximately 26.5% for the 2021-2022 influenza season and 30.2% for the 2022-2023 influenza season.[68] This includes uptake in those who are considered to be at risk of severe disease and healthcare workers. As such, the historical mean influenza vaccination uptake was estimated to be 28% in those aged 50 to 64 years.

To inform our analysis of the potential costs and benefits associated with extending the influenza vaccination programme to include those aged 50 to 64 years and not considered to be at increased risk of severe disease, we reported outcomes for a projected influenza vaccination uptake rate of 35%. This was an estimate based on historical uptake rates in Ireland and UK uptake rates for the same population group.[70] According to CSO data in Ireland, the projected population for those aged 50 to 64 years in 2023 is 914,379.[98] Assuming a projected vaccine uptake rate of 35%, the mean incremental cost of vaccination for the 2023-2024 season (compared to the recent vaccine uptake rate of 28%), was estimated at approximately €2.3 million (using a vaccine cost of €10 plus 23% VAT and including the fees for administering the vaccine). The incremental cost associated with alternative vaccine costs are reported in Table 4.3 in Chapter 4. Additionally, based on this increased in uptake, the estimated reduction in burden of (notified) disease was 77 (27 to 139) cases, 22 (7 to 43) hospital episodes and 136 (42 to 268) bed days. The corresponding estimated mean reduction in influenza-related hospital costs were estimated at €0.11 million (€0.03 million to €0.2 million). The uncertainty in the numbers reported is strongly influenced by the uncertainty in vaccine effectiveness as this fluctuates from year to year.

Given that there appears to be a trend of increasing rates of influenza, hospital discharges, hospital discharges which include an ICU stay and mortality in those aged 60 to 64 years, a decision could be made to limit the eligibility extension to one or two of the five-year age bands within those aged 50 to 64 years. Using the same assumptions around uptake and cost as above, the estimated total mean incremental cost would be €0.68 million if extended to those aged 60 years and older and €1.43 million if extended to those aged 55 years and older.

In considering a reduction in notified cases as a proportion of GP attendances, the analysis shows that if a 35% influenza vaccination uptake was achieved, this would result in approximately 77 fewer GP visits per season. It should be noted that this does not include influenza cases that are not notified, nor does it include ILI cases that present to the GP.

This analysis has a number of limitations. First, the analysis was conducted from the perspective of the HSE and as such only considered direct costs and benefits. The wider societal impact of vaccination was not assessed; for example, vaccination not

only protects the individual getting vaccinated, but it can also reduce the risk of passing infections on to others, including members of the community at higher risk of severe disease.[107] Moreover, studies have reported the potential direct and indirect benefits to employers as a result of occupational influenza vaccination programmes.[108-113]

In the absence of population-level data, this analysis assumed that risk of serious disease is evenly distributed in the population aged 50 to 64 years, so it is likely that the projected reductions in health resource use overestimate the benefit of expanded vaccine uptake.

Data relating to vaccination uptake rates were limited to those reimbursed by the HSE and were not disggregated according to the risk status of the individual. Thesedata exclude uptake outside the HSE programme, for example, where individuals or employers (as part of an occupational health scheme) pay for the vaccine privately.. The reported uptake rate is therefore an underestimate of the true uptake rate in this population. However, extending eligibility to those aged 50 to 64 years (in the general population) is unlikely to result in changes to employer practice around providing vaccination to employees. As such, it should not impact the incremental budget impact for the HSE as most employees within the target group will continue to avail of it through their employer.

While an uptake rate of 35% is considered achievable supported by an appropriate public health information campaign, this uptake rate is higher than historical uptake rates in Ireland. During the 2021-2022 season, the influenza vaccination programme was extended to include the target population for this analysis, but the uptake rate was approximately 27% for that season. Therefore, the projected uptake rate used in this analysis is open to uncertainty and if influenza vaccine doses were purchased to fulfil this projected uptake rate, it could result in wastage if a lower uptake rate was achieved.

National rates of influenza were derived from sentinel practice data. Although the sentinel practice network contains a large population sample, the observed number of cases of influenza in the age group of interest is small in absolute terms. A small change in the number of detected cases can have a notable impact on the extrapolated national estimate of incidence. For this reason, differences in the incidence of influenza between five-year age groups within the 50 to 64 year old age group should be interpreted with some caution. Furthermore, while there is a relatively consistent finding that incidence is highest in the 60 to 64 year olds, in some years the incidence is higher in 50 to 54 year olds than in 55 to 59 year olds. Rather than being an inconsistency, it points to the fact that these two age groups have a very similar incidence. 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 burden associated with influenza.

Another limitation is that HIPE data were reported by calendar year, whereas HPSC data are reported by influenza season. Additionally, our assumptions relating to the reduction in the burden of disease are based on a pro-rata application of what may happen given current vaccination practice. However, given that vaccination is voluntary, those who choose to get vaccinated may derive less benefit than those who do not because they may not be at increased risk and or may already be taking measures to limit their exposure. As such, the figures presented in relation to a potential reduction in burden of disease are closer to a best-case scenario than a worst-case scenario. This model does not account for the fact that increased vaccination uptake also has implications relating to onward transmission of influenza to other age groups. However, in the context of influenza, where vaccination uptake is so unpredictable, any model would be unlikely to accurately reflect what would happen in practice. Finally, due to time constraints, systematic reviews of the clinical effectiveness and safety of QIVs were not conducted. As such, the costs of addressing any safety issues were also not considered in this analysis. However, studies have shown that QIVs are well-tolerated with no serious adverse events reported.[114-117] In studies where adverse events are reported, they are typically mild to moderate (for example, headache or pain at injection site) and resolve within one to three days after onset.

5.2 Context for the findings

Influenza causes considerable economic burden internationally. A US study conducted before the COVID-19 pandemic reported that influenza accounted for 65% of the total economic burden caused by vaccine-preventable diseases.[118] In considering the economic burden of all diseases where vaccination may provide some protection, those aged 50 to 64 years contributed 67% of this economic burden. Moreover, unvaccinated individuals accounted for 76% of cases. It may have been the case that those vaccinated were very aware of their vulnerabilities and took additional measures to reduce their contact with potentially infectious individuals. In Ireland, using data from 2011 to 2016, a study of avoidable hospital admissions for ambulatory care sensitive conditions (ACSCs) reported that 39.0% of total ACSC bed days (n=339,613) were related to influenza and pneumonia.[119] In considering vaccine-preventable ACSCs, influenza and pneumonia accounted for 99.8% of such admissions. For those aged 18 to 64 years specifically, 11.0% of total bed days (n=222,936) were attributable to ACSCs, the greatest contributors to this figure were influenza and pneumonia.

Although hospitalisations are still the main driver in costs associated with influenza,[83] data from the US Centers for Disease Control and Prevention (CDC) show that those aged 50 to 64 years contribute considerably more to the number of cases and medical visits, when compared to older adults.[120] Moreover, in a systematic review of the economic burden of influenza among adults aged 18 to 64 years, the authors reported that the average total cost per case was higher in those aged less than 64 years than in those aged 65 years or older. This may be attributed to a greater proportion of indirect costs incurred by this population group due to higher employment rates. In considering hospitalisation costs at a population level, the authors reported that hospitalisation costs were higher in those aged 65 years or older than those aged 50 to 64 due to the increased incidence of hospitalisation with age.[83]

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.[67] 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. Figures from the US CDC show that adjusted vaccine effectiveness (against influenza A and B) ranges from 19% to 60%. In a modelling study conducted in the UK using data from the 2018-2019 season, adjusted vaccine effectiveness of a standard QIV (against laboratory-confirmed influenza A and B) in those aged 18 to 64 years was 32.0 (95% CI: −8.1 to 57.2).[105] The low and non-significant vaccine effectiveness may be explained by antigenic changes in circulating A(H3N2) viruses and egg adaption of the vaccine virus.[121] While cell-based QIVs were developed to overcome this issue in egg adaptation of the vaccine virus, there is limited evidence available to assess the effectiveness of these vaccines compared to their egg-based counterparts.[122]

Another factor influencing the effectiveness of influenza vaccination programmes is uptake.[123] 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. This means that those who get vaccinated may be self-selecting and may not be those most at risk of exposure and or severe disease.

In Ireland, uptake of seasonal influenza vaccination is much lower than that recorded in the UK. Figures from 2012-2013 show that uptake of seasonal influenza vaccine in those aged 65 years and older was 56.9% in Ireland compared to 74.0%

in the UK;[124] in healthcare workers, this value was just 17.6% in Ireland compared to 45.6% in the UK.[125] Uptake rates have reportedly increased in Ireland, with 2017-2018 data showing that uptake was 68.0% in those aged 65 years and older and 44.8% in healthcare workers.[119] More recent uptake data obtained from the HPSC to inform this HTA indicate that the total uptake rate for seasonal influenza vaccination in 50 to 64 year olds was approximately 27% for the 2021-2022 influenza season[126] and 30% for the 2022-2023 influenza season.[68] Of note, during the 2021-2022 influenza season, those aged 50 to 64 years were eligible for a free influenza vaccination regardless of their risk status. The uptake data suggest that this extension of eligibility did not result in a higher coverage, suggesting that uptake was largely limited to those normally eligible. While it is possible that the COVID-19 pandemic may have influenced behaviour and reduced uptake of the influenza vaccine, it coincided with a period of high uptake of the COVID-19 vaccination. Extending eligibility for influenza vaccination to all 50 to 64 year olds may not markedly increase coverage over what was achieved in the 2022-2023 influenza season. The uptake figures for the UK, which are in excess of 50% are unlikely to be achieved in Ireland without an extensive public health information campaign; as such, a projected uptake rate of 35% was used in the analysis. Moreover, the data used in this analysis were not disaggregated according to risk status. As such, a wide range of projected uptake rates were assessed to ascertain the potential costs and effects of extending vaccination eligibility.

In a systematic review of the barriers and attitudes towards influenza vaccine uptake in those aged 18 to 64 years,[127] the barrier most frequently agreed upon was a perception of a lack of knowledge about the vaccine. Trust in healthcare services was the most agreed upon promoter for influenza vaccine uptake. Another systematic review synthesised qualitative evidence on healthcare workers' perceptions and experiences of seasonal influenza vaccination. The authors reported several barriers to vaccine uptake, such as, concerns about side-effects, doubtfulness regarding vaccine effectiveness, and the belief that influenza is not a serious illness.[128] The authors of both reviews concluded that strategies to encourage uptake should be directed towards creating a better understanding of vaccines and their value through education.[127, 128] Similarly, guidance from the WHO suggests that improved uptake of public health interventions such as influenza vaccination can be facilitated by consistent and targeted information delivered through trusted channels of communication.[60]

In considering mechanisms to improve vaccine uptake, it should be acknowledged that healthcare resources (such as, staff, facilities and budgets) are finite and channelling resources into vaccination diverts them from other aspects of healthcare. As such, it is pertinent to review the organisational processes which underpin national vaccination programmes, and to consider mechanisms by which efficiency

and or access can be improved, or whereby primary care resources can be released. An example was the creation of regional COVID-19 vaccination centres, which alleviated pressures in the primary care setting. The potential for co-administration of vaccines is also an option. For example, those aged 50 years and older are eligible for an autumn COVID-19 booster in Ireland.[129] If the influenza vaccination programme is extended to include the target population of this rapid HTA, these individuals could receive both vaccinations during the same visit limiting any additional burden on healthcare capacity.

5.3 Conclusions

Annual seasonal vaccination can be effective in reducing the incidence of influenza, including the incidence of severe disease. However, there is substantial uncertainty in relation to the potential costs and benefits associated with expanding reimbursement of vaccination to those in the general population (that is, those not included in one of the existing eligible groups) aged 50 to 64 years. The estimated mean incremental cost to the HSE of expanding reimbursement for the 2023 to 2024 influenza season is approximately €2.3 million if uptake in those aged 50 to 64 years increases from 28% to 35%. However, as vaccination uptake increases, the risk profile of the vaccinated population may change, so that the additional benefits achieved are not proportional. In the context of the existing HSE Seasonal Influenza Vaccination Programme which provides access to free influenza vaccination to those at identified as being at increased risk of exposure or of severe disease there is a relatively modest absolute number of influenza-related hospitalisations in this age group. Given this, and the substantial year-on-year variability in vaccine effectiveness, the potential for a reduction in demand for hospital care is likely to be small, irrespective of the age-band selected within this age cohort.

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