Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Use of an enhanced inactivated influenza vaccine for those aged 65 years and older in the Seasonal Influenza Vaccination Programme:

Protocol for a Health Technology Assessment

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About the Health Information and Quality Authority

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.

1 Introduction

Seasonal influenza (more commonly referred to as influenza),[1] is an acute respiratory infection caused by influenza ribonucleic acid (RNA) viruses from the Orthomyxoviridae family.[2] There are four types of influenza viruses (A, B, C and D) of which two (A and B) are the predominant virus types causing disease in humans.[2] As such, influenza A and influenza B are the main focus in the context of seasonal influenza. Influenza A viruses are further categorised into subtypes, according to the combination of glycoproteins (hemagglutinin (HA) and neuraminidase (NA)) present on the surface of the virus. Currently, there are 18 HA (H1-H18) and 11 NA (N1-N11) subtypes, with influenza A(H1N1) and A(H3N2) most commonly circulating, causing annual seasonal influenza cases.[3] Influenza B viruses do not have sub-types, but instead have two antigenically distinct lineages, Victoria and Yamagata.[2] Influenza A and B circulate globally; in the Northern hemisphere, the period of circulation is typically from November to April and in the Southern hemisphere it is from June to October.[2]

Seasonal influenza is characterised by respiratory and systemic symptoms including fever, malaise, myalgia, headache, sore throat and nasal congestion.[4] Gastrointestinal symptoms such as nausea, vomiting and diarrhoea are also common. Diagnosis of influenza typically occurs in the community when the virus is known to be circulating. In most healthy individuals, seasonal influenza is self-limiting and symptoms typically resolve in three to seven days. Treatment for these individuals consists of antipyretics, adequate fluid intake and rest. However, certain individuals have an increased risk of severe disease and may require hospitalisation and or treatment with antivirals.[4] Groups at increased risk 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]

Seasonal influenza places considerable burden on the healthcare system and society in terms of morbidity, mortality, hospitalisations and absenteeism from school and work. The World Health Organization (WHO) estimates that seasonal influenza can affect up to 20% of the population annually, with severe influenza illness accounting for approximately three to five million cases annually, and up to 650,000 respiratory deaths globally.[1] Seasonal influenza is a preventable infectious disease and getting an annual influenza vaccination is the most effective preventive measure. Other preventive measures to compliment annual vaccination include personal protective measures such as avoiding close contact with infected individuals and good hand hygiene.[6]

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.[7] In Ireland, anyone can pay for an annual influenza vaccine. However, for the 2023 to 2024 influenza season, population groups eligible for a free annual influenza vaccine through the Seasonal Influenza Vaccination Programme are those:

- aged 65 years and older
- aged 2 to 17 years
- who are a healthcare worker
- who are pregnant
- living in a nursing home or other long-term care facility
- in regular contact with pigs, poultry or waterfowl
- with a health condition that puts them at higher risk of influenza (aged 6 months and older)
- living with someone who has a health condition that puts them at higher risk of influenza
- who are caring for someone who has a health condition that puts them at higher risk of influenza.[8]

There are two types of influenza vaccines, inactivated influenza vaccines (IIVs) which are administered intramuscularly and intranasal live attenuated influenza vaccines (LAIVs); the latter is used for prophylaxis of influenza in children and adolescents aged from 24 months to less than 18 years of age.[9] Trivalent vaccines (TIVs) are IIVs that contain three strains of influenza virus (two A strains and one B strain), and quadrivalent vaccines (QIVs) are IIVs that contain four strains of influenza virus (two A strains and two B strains).[10]

Each year, the WHO issue recommendations to vaccine manufacturers relating to the content, including the specific viral subtyping, of the seasonal influenza vaccines. In the Northern Hemisphere, these recommendations are typically published in February to inform the upcoming influenza season (that is, November the same year to April the following year). These recommendations are based on global surveillance data and are critical to the effectiveness of influenza vaccines.[10] However, due to ongoing evolution of the influenza virus, antigenic mismatch between the virus strains contained in the vaccine and those in circulation can occur.

As such, vaccine effectiveness can be suboptimal.[11] Another factor affecting vaccine effectiveness is the individual's immune response, which can be suboptimal due to an ageing or compromised immune system, for example, in older adults (aged 65 years or older) or those with an immunocompromising condition.[12] As such, new and enhanced influenza vaccines have been developed in an attempt to increase vaccine effectiveness. These comprise:

- adjuvanted IIV (aIIV) – IIV with an added adjuvant such as the oil-in-water emulsion MF59® to produce an enhanced immunological response
- high-dose IIV (HD-IIV) – IIV which contains a fourfold increase of HA per strain, (that is, 60µg) instead of 15µg of HA typically included in a standard dose IIV
- cell-based IIV (ccIIV) – IIV manufactured using mammalian cell-culture
- recombinant HA IV (RIV) – IV manufactured using recombinant HA proteins instead of egg-derived processes.[13]

In Ireland, guidance from the National Immunisation Advisory Committee (NIAC) states that aQIVs should be used for those aged 65 years and older;[14] standard, egg-based QIVs (SD-QIV) are recommended if aQIVs are not available. Currently, only SD-QIVs are reimbursed for this age group as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme.[15] In order to inform a decision as to whether enhanced IIVs should be reimbursed as part of the HSE Seasonal Influenza Vaccination Programme, the Department of Health requested that HIQA complete a health technology assessment (HTA) of using an enhanced IIV for those aged 65 years and older in the Seasonal Influenza Vaccination Programme.

This protocol aims to present the methods for estimating the burden of disease associated with influenza and assessing the clinical effectiveness, cost effectiveness and budget impact, ethical and patient and social aspects, and organisational changes associated with amending the Seasonal Influenza Vaccination Programme to include use of an enhanced IIV for those aged 65 years and older.

2 Aims and objectives

The overarching aim of this HTA is to estimate the clinical and cost effectiveness of universal vaccination with an enhanced IIV in those aged 65 years and older.

With consideration to the population aged 65 years and older, the specific objectives of this HTA are to:

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

3 Establishment of the Expert Advisory Group

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

4 Description of the technology

A description will be provided of the enhanced IIVs currently available for immunisation against influenza along with an overview of international practice with respect to influenza vaccination programmes for those aged 65 years and older.

A review will be undertaken to identify enhanced IIVs that are authorised either centrally through the European Medicines Agency or nationally by the Health Products Regulatory Authority in Ireland for immunisation against seasonal influenza. A high-level comparison of the characteristics of these vaccines will be provided. A review will also be undertaken of international influenza vaccination programmes for those aged 65 years and older to identify how such programmes are structured with respect to the type of influenza vaccine(s) recommended, (that is, TIVs, QIVs and or enhanced IIVs) and the reimbursement of those vaccines.

5 Epidemiology and burden of disease

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

In Ireland, the Health Protection Surveillance Centre (HPSC) in partnership with the Irish College of General Practitioners (ICGP) and the National Virus Reference Laboratory (NVRL) has established a network of 60 computerised general sentinel practices who report on a weekly basis the number of patients seen with influenza-like illness (ILI).[16] ILI is defined as 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. 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 detect if influenza A and or B viruses are circulating by testing the specimens received.[16] These data will be used to estimate the incidence of notified influenza cases and laboratory-confirmed influenza-related hospital admissions, hospital admissions that included a stay in intensive care and deaths. Data from the HPSC will also be used to inform seasonal influenza vaccination uptake in Ireland.[17] It is acknowledged that these data are limited to the reimbursement of influenza vaccination through HSE programmes, and exclude data relating to for example, private occupational programmes. Moreover, it should be noted that influenza vaccination uptake data may be skewed as there has been increased uptake in recent years in light of the COVID-19 pandemic. Consideration will therefore be given to trends in vaccine uptake. Data from the Hospitalised In-Patient Enquiry (HIPE) system will also be used to understand the nature of influenza hospitalisations (for example, requirement for admission to intensive care and length of stay). Cross-sectional analyses of nationally representative datasets and individual studies will be used if deemed appropriate. In the absence of Irish data, the best available estimates will be derived from the international literature.

The incidence of influenza and complications and hospitalisation associated with influenza will be used to determine the burden of the disease on both the Irish healthcare system and wider society. The review of epidemiological sources will also be used to inform the inputs to the economic model (described in section 7) and the estimated resources required to provide the appropriate level of care to the target population, that is, patients aged 65 years and older with influenza.

Estimation of the eligible population

Data on the total number of adults aged 65 years and older years will be sought from the Central Statistics Office (CSO). Based on projected population figures from the CSO, there are an estimated 819,143 adults aged 65 years and older living in Ireland in 2024.[18]

6 Literature reviews

Evidence in relation to influenza vaccination in those aged 65 years and older will be based on systematic reviews of the literature. Specifically, (1) a systematic review of the clinical effectiveness and safety of enhanced IIVs in those aged 65 years and older; (2) a review of economic evaluations of enhanced IIVs in those aged 65 years and older. Where a de novo review is undertaken, full details of the review will be outlined in a registered protocol on PROSPERO and the reporting of the reviews will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and national guidelines.[19-21]

6.1 Clinical effectiveness and safety

The HTA Directorate evaluation team previously completed a systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. This systematic review was completed under contract with the European Centre for Disease Prevention and Control (ECDC), who published it in August 2020.[13] This systematic review is being updated for the ECDC by researchers at the Robert Koch Institute and the findings of the updated systematic review will be used to inform the clinical effectiveness and safety chapter of this HTA.

6.2 Cost effectiveness

Economic evaluations of immunisation vaccination programmes vary in terms of the parameter costs (for example, vaccine ingredient and administration costs and treatment costs), outcomes (for example, reduction in cases and hospital

admissions), and perspectives considered (for example, payer and societal perspectives). An initial scan of the literature will be conducted to establish whether an existing systematic review(s) can be used to inform the model structure and inputs of an Irish-specific cost-effectiveness analysis (CEA), or whether a de novo rapid review is required. Any potentially applicable existing systematic reviews will be assessed for quality.[22] If a de novo rapid review is deemed as required, accepted methods for conducting a review of economic evaluations will be applied.[23, 24]

7 Economic evaluation

An economic evaluation comprising a CEA and a budget impact analysis (BIA) will be conducted. The CEA will be conducted from the perspective of the publicly funded health and social care system (HSE). In Ireland, the 'reference case' or preferred method in the primary analysis for HTA is to adopt the perspective of the publicly funded health and social care system. However, in circumstances where it may be appropriate to adopt a wider perspective, the guidance also provides for this possibility, but it must be clearly justified and supported by sufficient evidence.[25] It is argued that economic evaluations of vaccines should adopt a broader perspective than the healthcare payer perspective and should be conducted from the societal perspective to incorporate their full value.[26] The elements of vaccines that may be undervalued when a payer perspective is adopted include the prevention of complications, health gains for caregivers, herd effects, community benefits, enhanced productivity and the promotion of equity.[26] Furthermore, in the case of highly contagious diseases affecting a large cohort annually, productivity losses (associated with both paid and unpaid work) can be significant. Consideration will be given to also conducting the CEA from the societal perspective.

A summary of the model characteristics for each of the CEA and BIA is presented in Table 2.

Table 2 Model characteristics for CEA and BIA

Model characteristics	CEA	BIA
Perspective	Publicly-funded health and social care system (HSE)	Publicly-funded health and social care system (HSE)
Time horizon	Lifetime†	Five years
Discount rate	4% (costs and QALYs)* after the first year	N/A
Outcome	ICER or incremental net monetary benefit (INMB)	Incremental cost per annum
Sensitivity analysis	Probabilistic and deterministic	Probabilistic and deterministic

Key: BIA – budget impact analysis; CEA – cost-effectiveness analysis; HSE – Health Service Executive; ICER – incremental cost-effectiveness ratio; N/A – not applicable; QALY – quality-adjusted life year.
*Or the discount rate that applies at the time of publication.
†The time horizon for the analysis may be dependent on input parameters for clinical effectiveness and safety estimates which will be based on evidence from the systematic review.

7.1 Cost-effectiveness analysis

The CEA of universal vaccination with an enhanced inactivated influenza vaccine in those aged 65 years and older will be conducted in accordance with national HTA guidelines and reported in accordance with Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) reporting guidelines.[25, 27] It will be conducted from the perspective of the publicly funded healthcare system (HSE) over in a hypothetical patient cohort over a lifetime period with consideration also given to the presentation of the societal perspective. The primary outcome of the CEA will be an incremental cost-effectiveness ratio (ICER) expressed in terms of the mean cost per quality-adjusted life year (QALY) gained. A discount rate of 4% will be applied to costs and outcomes occurring after the first year. There is currently no accepted willingness-to-pay (WTP) threshold for non-pharmaceutical technologies in Ireland. However, WTP thresholds of between €20,000/QALY and €45,000/QALY are generally employed to interpret evidence of cost effectiveness.

A total of 13 different considerations have been identified for modelling and health economic evaluation of vaccination programmes specifically. These include model selection (static or dynamic), time horizon of models, natural disease history, measures of vaccine-induced protection, duration of vaccine-induced protection, indirect effects apart from herd protection, target population, model calibration and validation, handling uncertainty, discounting, health-related quality of life, cost components, and the perspective adopted.[28] The appropriate model structure will be informed by the results of the review of cost-effectiveness analyses. Estimates of the relative effectiveness of potential vaccination strategies generated from the updated systematic review of clinical effectiveness will be used to populate the economic model. Where possible, model inputs will be informed by national literature and data sources. In the absence of robust national data, data from

countries considered to be generalisable to the Irish setting may be a potential source of model input values. Where data from the literature are lacking or subject to considerable uncertainty, the expert input of the EAG will be required to inform suitable model input parameters.

The economic modelling will also require extensive sensitivity and scenario analyses to explore the key sources of uncertainty and how they impact on the conclusions of the economic analysis. This includes accounting for parameter uncertainty (e.g., costs), methodological uncertainty (e.g., transmission dynamics) and model uncertainty. Key drivers will be identified using deterministic sensitivity analysis. Additionally, there are a number of vaccine-specific features that require consideration in uncertainty analysis, including but not limited to, duration of immunity, vaccination coverage, and need for boosting. Based on the findings of the review of cost-effectiveness studies and input of the EAG, these will be examined in scenario analyses.

7.2 Budget impact analysis

The BIA will provide information for policymakers regarding the potential affordability of switching from universal vaccination with a standard IIV to an enhanced inactivated influenza vaccine in those aged 65 years and older. It will estimate the costs to the HSE associated with implementing the vaccination programme over an initial five-year time horizon, reported in terms of incremental annual cost. Estimates of budget impact will be particularly sensitive to uptake rates for the vaccination programme. A range of scenarios reflecting judgements on uptake rates for vaccination will therefore be considered in the BIA. For parameters that are unsupported by published literature, input from the EAG will be required to inform plausible values. In addition to the cost of the vaccines, changes to organisational processes will be identified and considered as part of the BIA. Furthermore, potential cost offsets, such as prevention of disease sequelae and hospitalisation, will also be considered and included, if appropriate.

8 Organisational considerations

The assessment of necessary organisational changes will be carried out in accordance with the EUnetHTA Core Model.[29] A description of the current vaccines used in the influenza vaccination schedule for those aged 65 years and older, any anticipated changes in the organisation of care as a result of universal vaccination with an enhanced IIV, and the resulting impact on existing activities will be provided. The impact of universal vaccination with an enhanced IIV in those aged 65 years and older on various types of resources (such as, human resources, equipment

and supplies, and facilities) and any additional associated healthcare interventions (for example, additional patient education and support services) will be considered. Estimated resource use (with consideration to the size of the eligible population) will be used to inform the relevant inputs to the BIA.

9 Ethical considerations

The ethical analysis will consider key social and moral norms and values relevant to vaccination programmes. Key ethical issues as outlined in the EUnetHTA Core Model will be used to guide the ethical analysis, under some or all of the following topic headings:[29]

- benefit-harm balance at both the individual and population level
- autonomy
- respect for persons
- justice and equity
- legislation
- ethical consequences.

10 Conclusion

Universal vaccination with an enhanced IIV in those aged 65 years and older in Ireland may represent a clinically effective and cost-effective intervention to reduce the burden of influenza on both health services and wider society. Given the anticipated costs and uncertainty around the potential benefits of enhanced IIVs in those aged 65 years and older, a HTA will be conducted to inform policy decisions in that regard. The HTA will comprise reviews of clinical effectiveness and cost effectiveness, a CEA, a BIA, and an assessment of the associated organisational, social and ethical aspects of universal vaccination with an enhanced IIV in those aged 65 years and older.

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