Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Herpes zoster vaccination for adults: Protocol for a health technology assessment

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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.

1 Introduction

Varicella-zoster virus is a herpes virus associated with two distinct clinical syndromes – varicella, commonly known as chickenpox and herpes zoster, commonly known as shingles. Primary infection results in varicella, after which the virus becomes latent and may reactivate after a period, typically several decades later, as herpes zoster.

Herpes zoster is typically recognised by a painful blistering rash on the torso. Although pain may persist for much longer, the average duration of the rash ranges from seven to 10 days, with the resulting scabs typically resolving completely within approximately two to four weeks.

The incidence rate of herpes zoster in Europe is estimated to be between 5.2 and 10.9 per 1,000 person-years.[1] Irish data indicate that typically a GP will see one to three cases of herpes zoster per month.[2] Herpes zoster mostly presents in patients aged 50 years and older and a study of primary care presentation in Ireland suggests the average age at presentation is between 60 and 70 years.[2] The risk of herpes zoster, and complications resulting from the disease, is higher in adults aged 50 years and older.[3] The increased risk in older adults is a result of waning cell-mediated immunity. Likewise, immunocompromised individuals are at an increased risk of herpes zoster and serious complications, due to diminished or loss of cell-mediated immunity.[4]

The most common complication of herpes zoster is post herpetic neuralgia (PHN).[5] PHN is persistent pain which lingers long after the initial rash and blisters have healed. PHN is associated with a significant impact on quality of life, affecting general activity, mood, sleep, and walking ability.[6] Up to 30% of individuals with HZ will develop PHN.[7] Factors that contributed towards this variation in PHN incidence across studies included differing definitions of PHN, differing study designs and the age distribution of the study populations. The risk of PHN is consistently reported to be higher in older patients.

2 Aims and objectives

The aim of this HTA is to estimate the clinical effectiveness and cost effectiveness of expanding the national adult immunisation programme to include herpes zoster vaccination.

The specific objectives of this HTA are to:

- describe the currently approved vaccines and vaccination options for immunisation against herpes zoster
- describe the epidemiology and burden of disease associated with herpes zoster in Ireland
- review the current evidence of the clinical effectiveness and safety of potential herpes zoster vaccination strategies for adults aged 50 years and over and adults aged 18 years and older who are at increased risk of herpes zoster
- review the current evidence of the cost effectiveness of herpes zoster vaccination programmes for adults
- assess the cost effectiveness and budget impact of including herpes zoster vaccination in the adult immunisation schedule.
- consider any potential organisational and resource implications of including herpes zoster vaccination in the adult immunisation schedule
- consider any ethical and social implications that adding herpes zoster vaccination to the adult immunisation schedule may have for patients, the general public or the healthcare system in Ireland
- based on the evidence in this assessment, provide advice to the Minister to support a decision on whether to include herpes zoster vaccination in the adult immunisation schedule in Ireland.

The HTA will be conducted in line with the HIQA quality assurance framework for HTA.

3 Establishment of the Expert Advisory Group

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

4 Description of the technology

A description of the vaccines currently available for immunisation against herpes zoster and an overview of international practice with respect to herpes zoster vaccination programmes for adults will be provided.

A review will be undertaken to identify herpes zoster vaccines that are authorised by either the Health Products Regulatory Authority in Ireland or centrally through the European Medicines Agency for immunisation against herpes zoster and which are marketed or distributed in Ireland.

A review of international herpes zoster programme for adults will be undertaken to identify how such programmes are structured with respect to:

- population or populations included (age and immune status)
- type of vaccine, that is, live or recombinant
- interval between doses where a two-dose schedule is in place.

Where reported, data will also be gathered on the rationale for the vaccination approach, the vaccine uptake rate, and if the country (or region) also provides a childhood varicella vaccination programme.

5 Epidemiology and burden of disease

A comprehensive description of the epidemiology of herpes zoster and burden of disease associated with herpes zoster will be provided. This section will be informed by a review of national and international literature and data.

Herpes zoster incidence in the community will be estimated from data obtained from the sentinel surveillance system of the Irish College of General Practitioners (ICGP)/ Health Protection Surveillance Centre (HPSC).[8] Data from the Hospitalised In-Patient Enquiry (HIPE) system will be sought to understand the nature of herpes zoster hospitalisations (for example, age profile, and average length of stay). Cross sectional analyses of nationally representative datasets and individual studies will be used if deemed appropriate. Where there is an absence of Irish data, the best available estimates will be derived from the international literature.

The incidence of herpes zoster and complications and hospitalisation associated with herpes zoster 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 for the budget impact assessment.

Estimation of the eligible population

The most recent Irish census data from the Central Statistics Office will be used to estimate the size of the eligible general population. For the adult population at increased risk of herpes zoster, data will be sought from existing adult immunisation programmes where relevant subgroups have eligibility.

6 Clinical efficacy, effectiveness and safety

Up-to-date evidence underpinning the use of herpes zoster vaccines is central to decision-making regarding the expansion of the national immunisation programme. This chapter will focus on primary vaccination and exclude studies that limit the use of herpes zoster vaccines to post-exposure prophylaxis. Accordingly, two research questions (RQ) have been formulated to establish the clinical efficacy, effectiveness and safety of herpes zoster vaccine:

RQ 1 – What is the clinical efficacy and effectiveness of the currently licensed and approved recombinant vaccine (Shingrix®) for the prevention of herpes zoster and associated complications, in adults aged 50 years and older and in adults aged 18 and over who are at increased risk of herpes zoster?

RQ 2 – What is the safety profile of the currently licensed and approved recombinant vaccine (Shingrix®) for the prevention of herpes zoster in adults aged 50 years and older and in adults aged 18 and over who are at increased risk of herpes zoster?

The live, attenuated zoster vaccine Zostavax® will not be included in this systematic review. In August 2023, Merck Sharp & Dohme, informed HIQA that based on a careful evaluation of the decline in clinical use and the availability of alternative vaccines, Merck Sharp & Dohme has made the decision to voluntarily discontinue manufacturing and supplying the herpes zoster vaccine, Zostavax® (Zoster Vaccine Live).[9]

A systematic review will be conducted. The reporting of the review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and national guidelines.[10, 11]

6.1 Inclusion criteria

The eligibility criteria for inclusion in the review were formulated according to the Population, Intervention, Comparator, Outcomes and Study Design (PICOS) framework. Table 1 outlines the eligibility criteria for the review of clinical efficacy and effectiveness and Table 2 outlines the eligibility criteria for the review of safety. The review of clinical efficacy will focus on comparative studies only, whereas the review of safety will also incorporate non-comparative studies. Non-comparative data will be presented separately.

Table 1 RQ 1 Clinical efficacy and effectiveness inclusion criteria

Criterion	Description
Population	Immunocompetent adults aged 50 years and older Adults aged 18 years and older who are at increased risk of herpes zoster, for example, immunocompromised individuals
Intervention	Vaccination with a vaccine against herpes zoster, approved and licensed for used within the European Union: Zoster vaccine (recombinant, adjuvanted) (brand name Shingrix®) (Studies that limit vaccine use to post-exposure prophylaxis will be excluded)
Comparators	▪ vaccination with an alternative vaccine against herpes zoster than that used as the intervention ▪ placebo or no vaccination ▪ different time interval for second dose ▪ concomitant administration with another vaccine.
Outcomes	Vaccine efficacy / effectiveness ▪ incidence of herpes zoster ▪ incidence of post-herpetic neuralgia (PHN) ▪ incidence of other complications associated with herpes zoster including herpes zoster ophthalmicus (HZO)

Criterion	Description
	▪ mortality associated with herpes zoster ▪ hospitalisation associated with herpes zoster ▪ quality of life using validated questionnaires ▪ duration of protection Subgroup ▪ differences in vaccine efficacy or effectiveness by age-group, and time since vaccination.
Study design	**Include:** Experimental studies ▪ randomised controlled trials ▪ quasi-randomised controlled trials ▪ non-randomised controlled trials. Quasi-experimental studies ▪ interrupted time series ▪ controlled before and after. Observational studies with a control group ▪ cohort studies ▪ case-control studies. **Exclude:** ▪ non-human studies ▪ observational studies without a control group ▪ letters, editorials, commentaries or preprints ▪ conference abstracts.

Key: RQ – research question.

Table 2 RQ 2 Safety profile inclusion criteria

Criterion	Description
Population	Immunocompetent adults aged 50 years and older Adults aged 18 years and older who are at increased risk of herpes zoster, for example immunocompromised individuals
Intervention	Vaccination with a vaccine against herpes zoster, approved and licensed for used within the European Union: Zoster vaccine (recombinant, adjuvanted) (Brand name Shingrix®) (Studies that limit vaccine use to post-exposure prophylaxis will be excluded)
Comparators	▪ vaccination with an alternative vaccine against herpes zoster than that use as the intervention ▪ placebo or no vaccination ▪ different time interval for second dose ▪ concomitant administration with another vaccine ▪ no comparator.
Outcomes	▪ adverse events at the injection site ▪ systemic adverse events ▪ serious adverse events (grade 3 & 4) ▪ withdrawal of participants as a result of adverse events ▪ potential immune-mediated diseases ▪ death.
Study design	Include: ▪ Experimental studies ▪ randomised controlled trials

Criterion	Description
	▪ quasi-randomised controlled trials. non-randomised controlled trials ▪ Quasi-experimental studies ▪ interrupted time series ▪ controlled before and after. Observational studies with a control group ▪ cohort studies ▪ case-control studies. Exclude: ▪ non-human studies ▪ case studies and case series ▪ letters, editorials, commentaries or preprints ▪ conference abstracts.

Key: RQ – research question.

6.2 Search strategy and information sources

A comprehensive electronic search will be performed in Embase (Elsevier), Medline (EBSCO) and the Cochrane Library. The search strings will be developed in consultation with an information specialist.

Searches will be limited to 2008 to current. The zoster vaccine (recombinant, adjuvanted) received marketing authorisation from the European Medicines Agency in 2018 and therefore this date limit allows for 10-years of data prior to marketing authorisation.

A search for ongoing clinical trials relevant to these RQs will also be conducted in clinical trials registries.

6.3 Study selection

Titles and abstracts of articles retrieved will be screened independently by two reviewers. The full text of potentially eligible articles will be retrieved and

independently assessed for eligibility by two reviewers according to the criteria outlined in section 6.1. A PRISMA flow diagram, outlining the study selection process, will be completed. Disagreements will be resolved through discussion, or if necessary, through involvement of a third reviewer.

6.4 Data extraction

Data extraction will be conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements in data extraction will be resolved through discussion, or if necessary, involvement of a third reviewer.

6.5 Quality assessment

Two reviewers will independently assess the quality of included studies. Risk of bias will be assessed using the Cochrane revised risk of bias tool for RCTs (RoB2).[12] The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool will be used to assess the quality of non-randomised studies.[13] An adapted version of the Newcastle-Ottawa Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies will be used for the appraisal of non-comparative studies.[14] Disagreements will be resolved through discussion, or if necessary, a third reviewer.

6.6 Data synthesis and analysis

Meta-analysis will be undertaken in accordance with Cochrane methodology.[15] Data will be presented separately for immunocompetent and at risk populations. Where feasible, meta-analysis of outcomes will be undertaken. Where meta-analysis is not considered appropriate, for example in the case of considerable clinical heterogeneity or a small number of events, outcomes will be synthesised narratively.

7 Economic evaluation

An economic evaluation comprising a cost-effectiveness analysis (CEA) and a budget impact analysis (BIA) will be conducted. 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, that is, the Health Service Executive (HSE). 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.[16] To incorporate their full value, it is argued that economic evaluations of vaccines should adopt a broader societal perspective rather than just that of the healthcare payer.[17] The elements of

vaccines that may be undervalued when a payer perspective is adopted include the potential prevention of complications, health gains for caregivers, herd effects, community benefits, enhanced productivity and the promotion of equity.[17] In order to incorporate the wider societal costs and benefits of herpes zoster vaccination, the CEA will be separately conducted from both the publicly-funded health and social care system (or payer) and wider societal perspectives.

A summary of the model characteristics for each of the CEA and BIA is presented in Table 3.

Table 3 Model characteristics for CEA and BIA

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

Key: BIA – budget impact analysis; CEA – cost-effectiveness analysis; HSE – Health Service Executive; ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; 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.

1.1. Review of economic modelling studies

Published economic evaluations of herpes zoster vaccination programmes vary in terms of model design, target population, included costs and outcomes and associated parameter values, vaccine parameter values and perspective adopted. A scoping review of the literature will be conducted to establish whether an existing systematic review(s) can be used to inform the model structure, inputs and parameter values of an Irish-specific CEA, or whether a de novo systematic review is required. The methodological quality of any potentially applicable existing systematic reviews will be assessed using the AMSTAR 2 tool.[18] If a de novo systematic review

is deemed necessary, accepted methods for conducting a systematic review of economic evaluations will be applied.[19]

7.1 Cost-effectiveness analysis

The CEA of expanding the immunisation schedule for adults in Ireland to include herpes zoster vaccination will be conducted in accordance with national HTA guidelines[16] and reported in accordance with Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.[20] It will be conducted from the perspectives of both the HSE and wider society in a hypothetical patient cohort over a lifetime period. 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 set willingness-to-pay (WTP) threshold for technologies in Ireland. However, WTP thresholds of between €20,000 and €45,000 per QALY gained are generally employed to interpret cost effectiveness. While these thresholds are used from a HSE perspective, they do not apply to ICERs from a societal perspective, for which there is no agreed WTP threshold.

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

- perspectives.[21]

The appropriate model structure will be informed by the results of the review of the economic modelling studies of herpes zoster vaccination. Estimates of the relative effectiveness of potential vaccination strategies generated from the systematic review of clinical efficacy and 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 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 modelling studies and input of the EAG, these may be examined in scenario analyses.

7.2 Budget impact analysis

The BIA will provide information for decision-makers regarding the potential affordability of expanding the immunisation programme for adults to include herpes zoster vaccination. It will predict 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 primarily influenced by 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 resulting from the addition of herpes zoster to the immunisation schedule 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.[22] A description of the current pathway for the delivery of other adult vaccinations, any anticipated changes in the organisation of care as a result of the introduction of herpes zoster vaccination to the immunisation schedule, and the resulting impact on existing activities will be provided. The impact of the provision of a herpes zoster vaccination programme 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.

9 Ethical considerations

The ethical analysis will consider key social and moral norms and values relevant to vaccination programmes. Key ethical issues in the EUnetHTA Core Model will be used to guide the ethical analysis, under some or all of the following topic headings:[22]

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

10 Dissemination

The evidence gathered, as outlined in sections 4 to 9, will be synthesised in a report to be published on the HIQA website. The findings of the report will inform HIQA's advice to the Minster for Health.

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