Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Expansion of the childhood immunisation schedule to include varicella (chickenpox) vaccination:

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

Varicella-zoster virus is a member of the herpesvirus group and is 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 remains in the body as a latent infection. The virus may reactivate after a period, typically several decades later, resulting in herpes zoster.

Varicella is a common, acute infectious disease, mainly affecting children, with one case of primary varicella potentially infecting 10 to 12 susceptible people.[2] The annual incidence of varicella in EU/EEA countries typically approximates the annual birth cohort;[1] the total number of births in Ireland in 2020 was approximately 56,000.[2] Varicella is typically mild, and although complications are uncommon in otherwise healthy children, they can and do occur and may require hospitalisation. Complications may include superinfection (usually with Group A streptococcus), skin scarring, and rarely encephalitis, pneumonia, glomerulonephritis, myocarditis, hepatitis and coagulopathy.[3] The most frequent complications are skin and soft tissue superinfections, followed by neurological and pulmonary complications.[1]

The World Health Organization (WHO) advises that the introduction of routine childhood varicella vaccination should be considered in countries where varicella is an important public health burden and resources are sufficient to ensure sustained vaccination coverage of at least 80% of the population.[4] Similarly, the European Centre for Disease Prevention and Control (ECDC) recommends that in considering the introduction of a varicella immunisation programme, individual countries should assess both their epidemiological and socioeconomic situations and their capacity to achieve high vaccination coverage.[1] In 2018, at least 36 countries and regions globally had introduced universal varicella vaccination, though not all programmes were publicly funded.[5] The established varicella vaccination programmes are heterogeneous, with a number of important differences between them as follows:

- dosing schedule, that is, a one- or two-dose schedule
- type of vaccine(s) administered (monovalent varicella only, quadrivalent measles, mumps, rubella, varicella (MMRV) vaccine only, or both where a two-dose schedule is in place)
- age at which the first dose is recommended
- time interval between vaccines where a two-dose schedule is in place.

In Ireland, varicella vaccination is not currently included as part of the routine

childhood immunisation schedule. It is only recommended for non-immune individuals without a definite history of varicella, proof of immunity or previous vaccination (from 12 months of age) in specific risk groups.[3] Clinical practice guidelines for chickenpox in pregnancy also recommend varicella vaccination in women who are not immune to chickenpox and are planning a pregnancy or receiving infertility treatment.[6]

Following a formal request from the Department of Health, with support from the National Immunisation Advisory Committee (NIAC), an expansion of the childhood immunisation schedule in Ireland to include varicella vaccination was prioritised for inclusion in the HIQA's Health Technology Assessment (HTA) Directorate's work plan. Given the potential significant organisational and resource implications associated with expanding the childhood immunisation schedule to include varicella vaccination, a full HTA will be conducted to inform the decision-making process.

This protocol aims to present the methods for estimating the burden of disease associated with varicella and assessing the clinical-effectiveness, cost-effectiveness and budget impact, ethical and social aspects, and organisational changes associated with an expansion of the childhood immunisation schedule to include varicella vaccination.

2 Aims and objectives

The overarching aim of this HTA is to estimate the clinical-effectiveness and cost-effectiveness of expanding the childhood immunisation schedule to include varicella vaccination.

The specific objectives of this HTA are to:

- describe the vaccines approved and vaccination options for immunisation against varicella
- describe the epidemiology and burden of disease associated with childhood varicella in Ireland
- review the current evidence of the clinical effectiveness and safety of potential varicella vaccination strategies for children
- review the current evidence of the cost-effectiveness of varicella vaccination programmes for children

- assess the cost-effectiveness and budget impact of expanding the childhood immunisation schedule in Ireland to include varicella vaccination
- consider any potential organisational and resource implications of expanding the childhood immunisation schedule to include varicella vaccination
- consider any ethical and social implications that an expansion of the childhood immunisation schedule to include varicella vaccination may have for patients, parents, the general public or the healthcare system in Ireland.

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. 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 of the vaccines currently available for immunisation against varicella and an overview of international practice with respect to varicella vaccination programmes for children will be provided.

A review will be undertaken to identify varicella vaccines that are authorised by either the Health Products Regulatory Authority in Ireland or the European Medicines Agency for immunisation against varicella and which are marketed or distributed in Ireland. A high-level comparison of the characteristics of these vaccines will be provided.

A review of international varicella vaccination programmes for children will be undertaken to identify how such programmes are structured with respect to:

- dosing schedule, that is, a one-dose or two-dose varicella vaccination schedule
- type of varicella vaccine(s) recommended, that is, a monovalent or quadrivalent vaccine or both vaccines where a two-dose schedule is in place
- age at which the first varicella vaccine dose is recommended

- interval between varicella vaccines where a two-dose schedule is in place.

5 Epidemiology and burden of disease

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

In Ireland, the Health Protection Surveillance Centre (HPSC), in collaboration with the Irish College of General Practitioners (ICGP) and the National Virus Reference Laboratory (NVRL) operates a surveillance system for infectious diseases. The varicella sentinel GP surveillance data are based on clinical consultations reported by the Irish sentinel GP network.[3] Complications from chickenpox are uncommon in childhood, but can and do occur, sometimes leading to hospitalisation. Hospitalised cases of varicella became notifiable in 2011 and these data are recorded in the Computerised Infectious Disease Reporting (CIDR) system, and reported to the HPSC. If possible, data from the Hospitalised In-Patient Enquiry (HIPE) system will also be used to understand the nature of varicella hospitalisations (e.g., complications of the disease 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 varicella and complications and hospitalisation associated with varicella 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 with varicella.

Estimation of the eligible population

Data on the total number of live births will be sought from the Central Statistics Office. Based on the total number of births in Ireland in 2020, the estimated eligible population for varicella vaccination would be approximately 56,000 children per annum.[2]

6 Literature reviews

Three reviews relating to varicella vaccination will be conducted: (1) an overview of reviews of the clinical efficacy and effectiveness of potential varicella vaccination strategies; (2) an overview of reviews of the safety of potential varicella vaccination strategies; and (3) a review of economic evaluations of varicella vaccination programmes for children. Where appropriate, full details of each 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.[7-9]

6.1 Clinical efficacy, effectiveness and safety

The research questions (RQs) for the clinical efficacy and effectiveness, and safety of potential varicella vaccination strategies have been formulated in line with the PICOS (population, intervention, comparator, outcome, study design) framework, outlined in Tables 6.1 and 6.2.

RQ 1: What is the clinical efficacy and effectiveness of alternative vaccination strategies for active immunisation against varicella in immunocompetent children?

RQ 2: What is the safety profile of alternative vaccination strategies for active immunisation against varicella in immunocompetent children?

Preliminary scoping identified a number of systematic reviews assessing the efficacy (a measure of how well vaccines work in a controlled trial)[10] and effectiveness (a measure of how well vaccines work in the real world)[10] of varicella vaccines that have been published over the last 40 years, with early reviews based on the monovalent vaccine and a one-dose schedule, while more recent reviews are based on both the monovalent and quadrivalent MMRV vaccines and one- and two-dose schedules. However, no single existing systematic review captured the range of possible vaccination strategies across multiple outcomes. Therefore, in order to assess the clinical efficacy and effectiveness, and safety of potential varicella vaccination strategies, two overviews of reviews will be undertaken to produce a comprehensive and comprehensible summary of the relevant evidence generated since the development of the first live attenuated monovalent varicella vaccine almost 50 years ago.[11]

Studies will be selected for inclusion based on the criteria outlined in Tables 1 and 2.

Table 1 PICOS for overview of reviews of clinical efficacy and effectiveness of alternative varicella vaccination strategies

Population	Immunocompetent children aged nine months to six years
Intervention	Vaccination with any monovalent varicella or quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine.
Comparators	▪ placebo or no vaccination ▪ alternative dosing schedule ▪ alternative dosing interval ▪ alternative age at vaccination ▪ co-administration with another vaccine ▪ no comparator.
Outcomes	**Efficacy / effectiveness** ▪ mortality associated with varicella ▪ hospitalisation associated with varicella ▪ severe varicella ▪ incidence of varicella ▪ incidence of breakthrough varicella ▪ long-term persistence of protection based on incidence of breakthrough varicella over time ▪ incremental vaccine effectiveness (e.g., for 2-dose versus 1-dose or for long versus short interval between doses).
Study design	**Include:** ▪ reviews with the following key characteristics: o a clearly stated set of objectives with an explicit, reproducible methodology o a systematic search of at least two databases that attempts to identify all studies that would meet the eligibility criteria o a systematic presentation, and synthesis, of the characteristics and findings of the included studies. ▪ reviews reporting on at least one outcome of interest. **Exclude:** ▪ reviews only reporting data on immunocompromised children ▪ reviews only reporting data on persons ≥ seven years of age at vaccination ▪ reviews that incorporate theoretical studies or text and opinion as their primary source of evidence ▪ reviews that are published as an abstract only ▪ eligible reviews that have been updated and the updated review is included.

Table 2 PICOS for overview of reviews of the safety of alternative varicella vaccination strategies

Population	Immunocompetent children aged nine months to six years
Intervention	Vaccination with any monovalent varicella or quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine.
Comparators	▪ placebo or no vaccination ▪ alternative dosing schedule ▪ alternative dosing interval ▪ alternative age at vaccination ▪ co-administration with another vaccine ▪ no comparator.
Outcomes	**Safety** Any safety data including, but not limited to: ▪ seizures/convulsions (febrile/afebrile) ▪ anaphylaxis ▪ disseminated vaccine-strain varicella zoster virus ▪ encephalitis/encephalopathy ▪ herpes zoster ▪ pneumonia ▪ meningitis ▪ idiopathic thrombocytopenic purpura ▪ hospitalisation for any effect of vaccination ▪ short-term effects of vaccination: o localised reactions at injection site (e.g., pain, redness, swelling) o systemic reactions (e.g., fever, varicella-like rash, vomiting, diarrhoea).
Study design	**Include:** ▪ reviews with the following key characteristics: o a clearly stated set of objectives with an explicit, reproducible methodology o a systematic search of at least two databases that attempts to identify all studies that would meet the eligibility criteria o a systematic presentation, and synthesis, of the characteristics and findings of the included studies. ▪ reviews reporting on at least one outcome of interest. **Exclude:** ▪ reviews only reporting data on immunocompromised children ▪ reviews only reporting data on persons ≥ seven years of age at vaccination ▪ reviews that incorporate theoretical studies or text and opinion as their primary source of evidence ▪ reviews that are published as an abstract only ▪ eligible reviews that have been updated and the updated review is included.

Search strategy, screening and data extraction

A comprehensive electronic search will be performed in Embase (Elsevier), Medline (EBSCO) and the Cochrane Library. The SYSVAC and PROSPERO registries will also be searched to identify relevant reviews and registered protocols for forthcoming systematic reviews. Electronic database searches will be supplemented by a grey literature search of the Trip database, Google Scholar and the International HTA database. The search strings will be developed in consultation with an information

specialist. Websites of HTA agencies and government health ministries from the countries ranked 1-50 in the Human Development Index,[12] and websites of a number of international health agencies, will be searched. A non-domain specific Google search will also be conducted.

Titles and abstracts of reviews retrieved using the search strategy and those from additional sources will be screened independently by two reviewers.

The full text of potentially eligible reviews will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Tables 1 and 2. Data extraction will be conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements in screening, study selection or data extraction will be resolved through discussion, or if necessary, a third reviewer.

Data synthesis and analysis

A flow chart describing the review selection process and a narrative summary of the characteristics of included reviews will be presented. Findings that are extracted from the included reviews will be synthesised narratively and where appropriate graphically presented. Summary output tables will be developed in accordance with the research questions, where overall findings of the overview of reviews will be presented. Overlaps of original research studies in each of the included reviews will be clearly indicated, described and measured using the corrected covered area (CCA) approach.[13]

Quality assessment

Two reviewers will independently assess the included studies for risk of bias, using the AMSTAR 2 “A MeaSurement Tool to Assess systematic Reviews, version 2” tool.[14] Disagreements will be resolved through discussion and, if necessary, a third reviewer.

6.2 Cost-effectiveness

Economic evaluations of childhood varicella vaccination programmes vary in terms of the costs (for example, vaccines, therapeutics, GP visit, hospital stay), outcomes (for example, reduction in cases, reduction in incidence, reduction in morbidity, long-term persistence of protection, incidence of vaccine adverse events), and perspectives considered (for example, payer and societal perspectives). 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 and inputs of an Irish-specific

CEA, or whether a de novo systematic review is required. Any potentially applicable existing systematic reviews will be assessed for quality using the AMSTAR 2 tool.[14] If a de novo systemic review is deemed as required, accepted methods for conducting a systematic review of economic evaluations will be applied.[15]

7 Economic evaluation

An economic evaluation comprising a cost-effectiveness analysis (CEA) and a budget impact analysis (BIA) will be conducted. The CEA will be conducted from both the payer perspective of the Health Service Executive (HSE) and a wider societal perspective. 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.[16] 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.[17] 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.[17] Furthermore, in the case of highly contagious childhood diseases affecting a large cohort annually, productivity losses (associated with both paid and unpaid work) can be significant, where parents or guardians need to take time from work to care for children who are infectious and or ill. Therefore, in order to incorporate the wider societal costs and benefits of vaccination, the CEA will be conducted from both a payer and societal perspective.

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 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 overviews of reviews.

7.1 Cost-effectiveness analysis

The CEA of expanding the childhood immunisation schedule in Ireland to include varicella 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.[18] 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 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 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 perspectives.[19] 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 overview of reviews 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 is 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 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 expanding the childhood immunisation programme to include varicella 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 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 resulting from the addition of varicella 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.[20] A description of the current pathway for the delivery of other relevant childhood vaccination programmes, any anticipated changes in the organisation of care as a result of the introduction of varicella vaccination to the immunisation schedule, and the resulting impact on existing activities will be provided. The impact of the provision of a varicella 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. 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 in the EUnetHTA Core Model will be used to guide the ethical analysis, under some or all of the following topic headings:[20]

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

10 Conclusion

An expansion of the childhood immunisation schedule in Ireland to include varicella vaccination may represent a clinically effective and cost-effective intervention to reduce the burden of varicella on both health services and wider society. Given the anticipated costs and uncertainty around the potential benefits of a varicella vaccination programme for children, an 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 introducing a varicella vaccination programme for children.

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