Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment of the addition of herpes zoster (shingles) vaccination to the adult vaccination programme

Publication date: 19 July 2024

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory body established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector of Social Services within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of permanent international protection accommodation service centres, health services and children's social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children's social services.
- **Health technology assessment** — Evaluating the clinical and cost effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health and social care services, with the Department of Health and the HSE.

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Foreword

Herpes zoster (HZ), which is commonly known as shingles, is typically recognised by a painful blistering rash on the torso. HZ is caused by reactivation of the varicella zoster virus. Primary infection with the varicella zoster virus results in varicella (commonly known as chickenpox) which typically presents in children. After varicella infections resolve, the virus remains and becomes latent in the body's nervous system. The virus may reactivate after a period of time, typically several decades later, resulting in HZ. HZ can occur at any age, with a lifetime risk of HZ of approximately 30% in those who have previously had varicella. The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to the persistence of chronic pain after the resolution of the acute rash.

Shingles vaccines are available in Ireland, but the Health Service Executive (HSE) does not currently provide free vaccination — people must pay to be vaccinated. The vaccines are designed to prevent shingles and its complications in adults. Internationally, there are differences between immunisation programmes against HZ with respect to the type of vaccine, level of public funding, the age group(s) eligible to be vaccinated, and the vaccination of individuals at increased risk of HZ.

The purpose of this health technology assessment (HTA) was to establish the clinical effectiveness, cost effectiveness and budget impact of an expansion of the adult immunisation programme in Ireland to include HZ vaccination.

Work on the HTA was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise the Evaluation Team during the course of the HTA. HIQA would like to thank the Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report. The draft report was published on the HIQA website for a six-week targeted and public consultation, after which is was updated based on feedback received. Details of the consultation are provided in the associated statement of outcomes report, also published on the HIQA website.

Dr Máirín Ryan

Deputy Chief Executive & Director of Health Technology Assessment

Health Information and Quality Authority

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment.

Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice and information.

The membership of the EAG was as follows:

Dr Colette Bonner	Deputy Chief Medical Officer, Department of Health
Dr Geraldine Casey*	Specialist in Public Health Medicine, Health Protection Surveillance Centre
Ms Celine Clarke	Head of Advocacy and Public Affairs, Age Action
Dr Norma Donlon*	Senior Medical Officer, Health Protection Surveillance Centre
Ms Christina Donnelly	National Coordinator, Chronic Pain Ireland
Dr Patricia Harrington	Deputy Director of HTA Directorate, HIQA
Dr Lucy Jessop^{Y}	Consultant in Public Health Medicine, Director of the HSE National Immunisation Office
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Ms Susan O'Donnell	Professional Services Pharmacist, Irish Pharmacy Union
Ms Joan Quigley	Head of Assessment, HTA Directorate, HIQA
Dr Eve Robinson*	Specialist in Public Health Medicine, Health Protection Surveillance Centre
Ms Grainne Ryan	Public Health Nursing, HSE
Dr Máirín Ryan (Chair)	Director of HTA and Deputy CEO, HIQA
Dr Corinna Sadlier	Special Advisor, National Immunisation Advisory Committee
Dr Conor Teljeur	Chief Scientist, HTA Directorate, HIQA

Ms Gillian Walsh	Technical Researcher, National Immunisation Advisory Committee

*Dr Geraldine Casey attended the first EAG meeting in November 2023 as a representative of the HPSC and was replaced by Dr Norma Donlon prior to the second EAG meeting. Dr Norma Donlon left the HPSC in May 2024 and was replaced on this EAG by Dr Eve Robinson.
ϒDr Aparna Keegan attended the first and second EAG meeting as representative of the National Immunisation Office, and was replaced by Dr Lucy Jessop in May 2024.

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

- National Immunisation Advisory Committee
- Health Protection Surveillance Centre
- The Primary Care Reimbursement Service
- Hospital In-Patient Enquiry

Members of the Evaluation Team:

Members of HIQA's Evaluation Team were Joan Quigley, Susan Ahern, Dr Emma Reece, Orla Jenkins, David Byrne, Aoife Bergin, Dr Carol Mc Loughlin, Ellen Reidy, Marie Carrigan, Dr Patricia Harrington, Dr Conor Teljeur, and Dr Máirín Ryan.

Conflicts of Interest

Chronic Pain Ireland has declared that they received less than 10% of their funding from Grunenthal Pharma Ltd and from Accord Pharmaceuticals in 2021 and 2022. Grunenthal Pharma Ltd and Accord Pharmaceuticals market treatments for chronic pain in Ireland. Chronic Pain Ireland's chairperson was a spokesperson for the *Understanding Shingles Campaign by Glaxo SmithKline in association with Chronic Pain Ireland* which involved press, radio interviews and TV advertising throughout 2022 and 2023. Glaxo SmithKline market a shingles vaccine, Shingrix®, in Ireland.

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.

The Irish Pharmacy Union (IPU) receives advertising revenue from the pharmaceutical industry through its publication, IPU Review.

General practices and pharmacies derive a small portion of their income from administration of vaccines.

There were no reported potential conflicts of interest for members of the evaluation team.

Advice to the Minister for Health and the Health Service Executive

Following a request from the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) of the inclusion of herpes zoster (HZ) vaccination in the adult immunisation programme in Ireland. This HTA aimed to assess the clinical effectiveness and safety of HZ vaccination, as well as the cost effectiveness, budget impact, ethical and social aspects, and organisational changes associated with the introduction of a HZ vaccination programme for adults.

The key findings of this HTA, which informed HIQA's advice, were:

- The 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, which typically presents in children. After this, the virus becomes latent (dormant) and may reactivate, often several decades later, as shingles. Among those with a history of varicella, the individual life-time risk of developing HZ is approximately 30%.
- Shingles usually presents as a painful, blistering rash on the torso. Although pain and complications can persist for much longer, the rash typically lasts for a period of seven to 10 days, resolving completely within two to four weeks.
- The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to persistent chronic pain after the resolution of the acute rash. Other complications can include herpes zoster ophthalmicus affecting the eye, herpes zoster oticus affecting the ear, disseminated or recurrent HZ skin lesions, as well as neurological and cardiac complications.
    - PHN can significantly alter individuals' lives, inflicting debilitating pain, disrupting daily activities, sleep, and emotional wellbeing. In some individuals, it can lead to profound lifestyle changes, affecting relationships, work, and overall quality of life.
    - There is no reliable method to estimate the burden of PHN in Ireland.
    - International data suggest:
        - Substantial variability in the proportion of HZ cases that develop PHN. Factors that contribute to the wide range of estimates may include differences in the case definition of PHN, varying prevalence of other risk factors, or differences in population demographics or study design.

    - The probability of PHN increases with age, increasing from 0.10 (a one in 10 chance) in 50- to 59-year-olds to 0.21 (one in five) in those aged over 80 years.
    - Of those that develop PHN, symptoms can persist for a year or more in up to 5% to 10% of cases.
- In those with a primary diagnosis of HZ, Irish public acute hospital data for the ten-year period from 2013 to 2022 indicate:
    - A mean of 285 patient discharges and 2,626 bed days per annum, with almost 75% of discharges and 87% of bed days occurring in people aged over 50 years.
    - When stratified by five-year age-band, the mean number of discharges per year was highest (mean 40, range 26 to 53) and average length of stay longest (14.9 days) for those aged 85 years and older.
    - There were a total of 54 deaths in acute hospitals; 85% were in those aged 75 years and older, with almost half (46%) of all deaths occurring in those aged 84 years and older. These figures do not include individuals who may have died in the community as a result of HZ.
- At the time of undertaking the HTA, there were two vaccines licensed in Europe for the prevention of HZ and its most common complication, post-herpetic neuralgia: a live attenuated vaccine (ZVL) and a recombinant adjuvanted vaccine (RZV). The vaccines are both authorised for use in adults aged 50 years and older. RZV is additionally authorised for use in adults aged 18 years and older at increased risk of HZ. The ZVL vaccine is being voluntarily discontinued by the manufacturers, with a plan to cease production and distribution in 2024; as a result, ZVL was not considered in this assessment.
    - RZV requires two doses. The recommended interval between doses is two months; however, the second dose can be administered between two and six months after the first dose.
- The National Immunisation Advisory Committee (NIAC) recommend HZ vaccination at 65 years and over, due to the greater burden and severity of disease and PHN in this age group. Additionally, NIAC recommend RZV be considered in those aged 18 years and older at increased risk of herpes zoster, with the following subgroups noted: adults aged 50 years and over with immunocompromising conditions; HSCT recipients aged 18 years and over; solid organ transplant recipients aged 18 to 49 years; those with haematological malignancies aged 18 to 49 years; and those with uncontrolled HIV aged 18 to 49 years.
- A review of international practices was undertaken. This highlighted that while some countries have introduced immunisation programmes against HZ, there are differences among immunisation programmes against HZ with respect to the type of vaccine, level of public funding, the age group(s) eligible to be vaccinated, and

the vaccination of individuals at increased risk of HZ. A decision to provide public funding may have been conditional on confidential price reductions from the manufacturer. As such, the programmes may also differ in the negotiated vaccine prices.

- A systematic review was undertaken of the clinical efficacy, effectiveness and safety of RZV for the prevention of HZ and associated complications, in adults aged 50 years and older and in adults aged 18 years and older who are at increased risk of HZ. Overall, 20 RCTs (n=47,414), 12 observational cohort studies (n=47,424,636), seven single-arm trials (n=10,230) and 11 single-arm observational studies (n≈546,416) were included.
    - Considering the efficacy and effectiveness of RZV in the general population aged 50 years and older:
        - Vaccine efficacy in preventing HZ was estimated at 92% based on combined randomised control trial (RCT) data (3.8 years follow-up), and 70% based on observational data (up to two years follow-up).
        - Among individuals who develop HZ, no difference in risk of PHN was observed in combined RCT data. A protective effect against PHN for those who had been vaccinated (RR 0.39, 95% CI 0.30 to 0.50) was identified in a large observational cohort study.
        - In the general population aged 50 years and over, there was evidence of waning effectiveness, with data from two RCTs with long-term follow-up indicating that efficacy reduced from an initial 97.7% at year one to 73.2% by year 10.
    - For those at increased risk of HZ, vaccine efficacy in preventing HZ was reported by two RCTs; efficacy was 68.2% in haematopoietic stem cell transplant (HSCT) recipients and 87.2% in those with haematological malignancies.
    - Considering the safety of RZV:
        - Serious adverse events are uncommon, with RCT data suggesting that the incidence is similar in vaccine and placebo groups.
        - Local and systemic reactions are common. RCT data indicate that these are more frequent in vaccinated cohorts, and are generally transient and mild to moderate in intensity. The most frequent reactions reported are pain at the reaction site, fatigue and myalgia.
- An economic model was developed to estimate the cost effectiveness of HZ vaccination for adults at a range of different age year groups in the general population. Each strategy was based on vaccinating only those turning that age in a given year, rather than everyone that age and older.
    - The economic model considered an ex-wholesale cost of €151 per vial (dose) in the base case in addition to vaccine administration costs. At a

cost of €151 per vial, the incremental cost-effectiveness ratios (ICERs) ranged from €127,825 per quality-adjusted life year (QALY) for vaccination of those turning 80 years old, to €979,815 per QALY for vaccination of those turning 50 years old. Therefore, at this vaccine cost, HZ vaccination would be considered not cost effective. Based on the assumptions in the model, the vaccine cost would need to be less than €30 per dose for HZ vaccination at 75 and 80 years old to be cost effective at a willingness-to-pay threshold of €45,000 per QALY. The results of the economic evaluation were robust to probabilistic and one-way sensitivity analysis and various scenario analyses.

- The budget impact of HZ vaccination for various one-year age groups in the general population and a cohort of immunocompromised adults aged 18 years and older was estimated.
    - The estimated five-year incremental budget impact of an HZ vaccination programme with 50% uptake for adults in the general population ranged from €15.1 million for vaccination of 85-year-olds to €53.3 million with vaccination of 65-year-olds (one year age group only). Offering the vaccine to everyone over a certain age will incur a substantially larger budget impact than a single year of age. For example, if everyone aged 65 and over was offered the vaccine as recommended by NIAC, with 50% uptake the five-year budget impact would be €218 million.
    - The five-year incremental budget for eligible immunocompromised persons as recommended by NIAC (with 100% coverage) was estimated at €56.2 million. This estimate comprised €46.3 million for the cohort aged 50 years and older with non-specific immunocompromising conditions, €6.3 million for those with haematological malignancies, €2.2 million for solid organ transplant recipients, €745,000 for HSCT recipients and approximately €630,000 for those with advanced/untreated HIV. For all cohorts, the incremental budget impact in year one was significantly greater than years two to five as it was assumed that all those currently eligible for vaccination (the prevalent population) would be vaccinated in year one.
- A decision to fund the RZV vaccine as part of the adult programme could have significant financial and logistical implications depending on the population group for whom the vaccine is funded. For example, a staggered roll-out approach to RZV vaccination would be required if RZV vaccination was extended to all individuals included in the NIAC recommendations (n= approximately 850,000 in the first year and 53,000 each year after that). If funding was limited to specific subgroups of immunocompromised individuals, engagement with clinical specialists in tertiary services would be required to identify eligible individuals

and support uptake. Additional steps would also be required to track and contact people about their second dose given the two-dose schedule.

- Evidence from this HTA highlights that, based on current data, vaccinating adults in the general population over the age of 50 years against HZ is not cost effective and is associated with a substantial budget impact. The healthcare budget is finite; including HZ vaccination in the adult immunisation programme could require reallocation of resources, potentially impacting the existing healthcare system by diverting resources from other more cost-effective interventions or from the overall healthcare fund. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity costs (the value of the next best alternative forgone) of new investments are considered. This may prove difficult as there may be many competing claims requiring prioritisation of care. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens.

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

- Herpes zoster (HZ), commonly known as shingles, is characterised by a painful, blistering rash that typically takes two to four weeks to resolve. Among those with a history of varicella (chicken pox), the individual life-time risk of developing HZ is approximately 30%. The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to persistent chronic pain after the resolution of the acute rash. PHN can significantly alter individuals' lives, inflicting debilitating pain, disrupting daily activities, sleep, and emotional well-being. The probability of PHN after HZ increases with age, increasing from a one in 10 chance in 50- to 59-year-olds to one in five in those aged over 80 years.
- Both the risk of HZ and complications from HZ increase with age after 50 years and among individuals who are immunocompromised due to immunosuppressive conditions or therapies.
- There is clear and consistent evidence that the recombinant adjuvanted vaccine (RZV) vaccine is safe and effective at reducing HZ cases, but that its effectiveness diminishes over time. While local and systemic adverse events are common, serious adverse events are uncommon.
- At the submitted price, the current evidence suggests that HZ vaccination does not represent an efficient use of healthcare resources in Ireland.
    - The incremental cost-effectiveness ratios (ICERs) for the general population ranged from €127,825 per quality-adjusted life year (QALY)

gained for vaccination at age 80, to €979,815 per QALY gained for vaccination at age 50.
    - Based on the assumptions in the model, at a willingness-to-pay threshold of €45,000 per QALY, the vaccine cost would need to be reduced by at least 80% for HZ vaccination at age 75 or at age 80 to be cost effective.
    - Considering a vaccine uptake of 50%, the five-year incremental budget impact of a HZ vaccination programme for:
        - adults as they turn 65 years old (no catch-up for older adults) would be €53.3 million.
        - all adults aged 65 years and older as recommended by the National Immunisation Advisory Committee (NIAC) would be €218 million.
    - The five-year incremental budget for eligible immunocompromised persons as recommended by NIAC (with 100% coverage) was estimated at €56.2 million. This estimate comprised €46.3 million for the cohort aged 50 years and older with non-specific immunocompromising conditions, and €9.8 million for specific groups including those with haematological malignancies, solid organ transplant recipients, haematopoietic stem cell transplant (HSCT) recipients and those with advanced/untreated HIV.
- A decision to fund the RZV vaccine as part of the adult programme could have significant financial and logistical implications depending on the population groups for whom the vaccine is funded. RZV vaccination is given as a two-dose schedule. A staggered roll-out approach would be required if vaccination was extended to all individuals included in the NIAC recommendations (approximately 850,000 in the first year and 53,000 each year after that).
- While the addition of the HZ vaccine to the adult immunisation programme would improve equity of access to this vaccine, the use of resources in this way may create inequity in other areas of the healthcare system. In the context of a finite healthcare budget, it could require reallocation of resources potentially impacting the existing healthcare system by diverting resources from other effective treatments or from the overall healthcare fund. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens.

Executive summary

1. Introduction

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.

HIQA undertook this assessment of adding herpes zoster (shingles) vaccination to the national immunisation programme for adults at the request of the Department of Health following a recommendation from the National Immunisation Advisory Committee (NIAC). The aim of the HTA was to establish the clinical effectiveness, cost effectiveness and budget impact of the addition of herpes zoster (shingles) vaccination to the adult immunisation programme in Ireland. This assessment provides advice to the Minister for Health to inform a decision on whether to include herpes zoster vaccination in the adult immunisation programme in Ireland.

2. Description of the technology

There are two vaccines licensed in Europe for the prevention of herpes zoster (HZ) and its most common complication, post-herpetic neuralgia: a live attenuated vaccine (ZVL) and a recombinant adjuvanted vaccine (RZV). The vaccines are authorised for use in adults aged 50 years and older while RZV is also authorised for use in adults aged 18 years and older at increased risk of HZ. While both vaccines are licensed and marketed in Ireland, neither is currently funded by the HSE. The ZVL vaccine is being voluntarily discontinued by the manufacturers, with a plan to cease production and distribution in 2024; as a result, ZVL was not considered in this assessment. Internationally, there are differences among immunisation programmes against HZ with respect to the type of vaccine, level of public funding, the age group(s) eligible to be vaccinated, and the vaccination of individuals at increased risk of HZ. As of 8 January 2024, vaccination against HZ for adults in the general population was recommended and publicly funded in five countries in the EU and partially funded in one. A decision to provide public funding may have been conditional on confidential price reductions from the manufacturer. As such, the programmes may also differ in the negotiated vaccine prices. Beyond countries in the EU/EEA, Australia, New Zealand, Switzerland, and the United Kingdom (UK) also fund the vaccine within their national immunisation programmes, and funding depends on the state and province in the USA and Canada, respectively. The age at which adults in the general population are eligible for HZ vaccination is 65 years or older in the majority of these countries. For those at increased risk of HZ,

vaccination is variably offered from age 18 years or from age 50 years, with a number of countries specifying that funding is limited to those who are severely immunosuppressed or identifying the categories of patients for whom vaccination is funded.

3. Epidemiology and burden of disease

Herpes zoster (HZ) is a disease that results from the reactivation of latent varicella zoster virus in the body's nervous system. Typically characterised by a painful, blistering rash, it is often associated with acute pain and itching. Among those with a history of varicella, the individual life-time risk of developing HZ is approximately 30%. Complications of HZ disease can be extensive and can contribute to morbidity and mortality. Both the risk of HZ and complications from HZ increase with age after 50 years and among individuals who are immunocompromised due to immunosuppressive conditions or therapies.

Health Protection Surveillance Centre (HPSC) data from the sentinel GP surveillance programme for HZ were used to estimate rates of HZ episodes in primary care. Data from 2013 to 2022 indicate that rates of HZ episodes increased with age; mean rates were highest in those aged 75 to 79 years old (826 per 100,000 population). Based on public acute hospital data in Ireland, from 2013 to 2022 there were an average of 285 patient discharges and 2,626 bed days per annum, with almost 75% of discharges and 87% of bed days occurring in people aged over 50 years. The mean number of discharges per year was highest for those aged 84 years and older (mean 40, range 26 to 53), and the longest average length of stay was in those aged 84 years and over (14.9 days). In the period 2013 to 2022 there were 54 deaths in acute hospitals; 85% were in those aged 75 years and older, with almost half (46%) of all deaths occurring in those aged 84 years and older. These figures do not include individuals who may have died in the community as a result of HZ.

International data show that those who are immunocompromised have an increased incidence of HZ and severe disease compared to the general population. Incidence rates are highest in those undergoing haematopoietic stem cell transplant and solid organ transplant. Although mortality rates increase with increasing age, the overall HZ-mortality rate in Europe is generally low.

The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to the persistence of chronic pain after the resolution of the acute rash. Other complications can include herpes zoster ophthalmicus, herpes zoster oticus, disseminated or recurrent HZ lesions, as well as neurological and cardiac complications. There is substantial variability in the proportion of HZ cases that go on to develop PHN. This may in part relate to differences in the definition of PHN — for example, persistent pain that lasts at least 30 days after the acute infection or

pain lasting for 90 days or longer following resolution of the acute skin lesions. International data indicate that the probability of PHN at 90 days increases with age. On the basis of a large Spanish study, the probability increases from 0.10 (a one in 10 chance) in 50- to 59-year-olds to 0.21 (one in five) in those aged over 80 years. There is uncertainty over how long PHN symptoms persist; studies which measured those who had PHN at 90 days found that between 4% and 24.6% still experienced severe pain at nine months.

HZ and associated complications such as PHN can contribute significant care and cost burden on both primary care and acute hospital services. Data from international studies suggest mean costs increase with age and are consistently higher for individuals who experience complications of HZ (such as PHN) compared with those who do not, and for individuals identified to have immunocompromising conditions compared with those who do not.

4. Clinical efficacy, effectiveness and safety

A systematic review was undertaken of the clinical efficacy, effectiveness and safety of RZV for the prevention of HZ and associated complications, in adults aged 50 years and older and in adults aged 18 years and older who are at increased risk of HZ. Overall, 20 RCTs (n=47,414), 12 observational cohort studies (n=47,424,636), seven single-arm trials (n=10,230) and 11 single-arm observational studies (n≈546,416) were included. All of the RZV evidence considered related to Shingrix®, as this was the only RZV vaccine licensed in Europe at the time of writing.

For the general population aged 50 years and older, the vaccine efficacy in preventing HZ for RZV was estimated at 92% based on the combined RCT data (3.8 years follow-up), and 70% based on observational data (up to two years follow-up). In the general population aged 50 years and over, there was evidence of waning effectiveness, with data from two RCTs with long-term follow-up indicating that efficacy reduced from an initial 97.7% at year one to 73.2% by year 10. There was considerable uncertainty regarding the impact of age on efficacy and effectiveness due to limited data in age subgroups.

It is difficult to assess whether RZV vaccination prevents HZ-associated complications in individuals that develop breakthrough HZ due to limited data and inconsistency of the available data. The evidence in regards to the impact that RZV vaccination has on the quality of life in those who develop HZ after vaccination is limited. However, there was a reduction in the severity of illness, burden of illness and the duration of clinically significant pain.

For those at increased risk of HZ, vaccine efficacy in preventing HZ was reported by two RCTs; efficacy was 68.2% in haematopoietic stem cell transplant recipients and 87.2% in those with haematological malignancies.

In terms of safety, RZV was more reactogenic than placebo; solicited local and systemic reactions were more frequent in the vaccinated cohorts compared with the placebo cohorts. RCT data suggest that the reactions are generally transient and mild to moderate in intensity; the most frequent reactions reported were pain at the reaction site, fatigue and myalgia. The incidences of potential immune-mediated disease (pIMDs), serious adverse events (SAEs) and fatalities were similar in vaccine and placebo groups. One death was reported as vaccine-related in a participant with pre-existing thrombocytopenia.

RCT data suggest that adults who are at increased risk of HZ experience greater numbers of reactogenicity events, both local and systemic, post-RZV vaccination compared with placebo. Rates of adverse events, SAEs and pIMDs in those who are at increased risk of HZ were similar in RZV and placebo arms; however, they varied by population. No deaths were recorded as related to the vaccine in this group.

The overall quality of RCTs, as judged by the ROB2 tool, was deemed at low risk of bias in half of the included trials. Overall quality of observational trials, as assessed using the ROBINS-I tool, was moderate risk of bias with one study at serious risk of bias.

In summary, there is clear and consistent evidence that the RZV vaccine is effective at reducing HZ cases. Although RZV is initially effective, it is associated with waning immunity. The vaccine is effective in those aged over 18 years considered at increased risk of HZ, although effectiveness might be slightly lower in these populations than the adult general population aged over 50 years. While local and systemic adverse events are common with RZV, SAEs are uncommon.

5. Rapid review of methodology for economic modelling studies of herpes zoster vaccination

The most recent systematic review of economic modelling studies of routine herpes zoster (HZ) vaccination in high-income countries was published in 2019. To establish and assess the most up-to-date international evidence on the approaches taken to the economic modelling of HZ vaccination, a rapid review of studies published since 2018 was undertaken. Eighteen additional studies were identified in the rapid review. Combined with the 2019 systematic review, this identified 45 studies published between 2001 and 2023.

With similar characteristics observed among reviews, 23 studies were conducted for European countries, 15 for North America and seven for the Asia-Pacific region.

Eighteen studies were funded by industry; 13 by governments, government agencies and or research bodies; 10 declared no funding, while four did not declare details related to funding.

Thirty-two of 45 studies employed a Markov model, with a variety of model types employed in the remainder of studies. Multiple perspectives were adopted in 36% of studies. A total of 38% of studies used a societal perspective only, while 24% were from a payer perspective only. Recent studies were noted to adopt a more comprehensive approach to vaccination age scenarios, incorporate broader health outcomes and incorporate vaccine-related adverse events.

While overall the appraisal did not raise major concerns with the quality of included studies, there were some concerns with regard to the time horizon adopted, the level of detail provided for parameter data, the comprehensiveness of the assessment of uncertainty, and the description of model validation. This rapid review identified several notable modelling features for consideration in the development of a de novo economic model of HZ vaccination for Ireland. These include incorporating monthly Markov cycles to better reflect the natural disease course, including a broader range of health outcomes such as complications other than post-herpetic neuralgia, and incorporating the impact of vaccine-related adverse events.

6. Economic Evaluation

An economic model was developed to estimate the cost effectiveness and budget impact of herpes zoster (HZ) vaccination for adults in the general population aged 50 years and older. The budget impact of HZ vaccination for a cohort of immunocompromised adults aged 18 years and older was also estimated. Eight alternative two-dose HZ vaccination strategies, with vaccination at 50, 55, 60, 65, 70, 75, 80 and 85 years of age, were assessed. Each strategy was based on vaccinating only those turning that age in a given year, rather than everyone that age and older. Model parameters including disease incidence rates, vaccine effectiveness, transition probabilities, costs and utility values were estimated from a variety of published sources and national datasets for Ireland.

From both the payer and societal perspectives, the incremental cost-effectiveness ratios (ICERs) for all HZ vaccination strategies assessed in the general population, exceeded willingness-to-pay thresholds of €20,000 and €45,000 per quality-adjusted life-year (QALY) gained. At a vaccine cost of €151 per dose, the ICERs ranged from €127,825 per QALY for vaccination at 80 years old, to €979,815 per QALY for vaccination at 50 years old. Therefore, at this vaccine cost, HZ vaccination would be considered not cost effective. Based on the assumptions in the model, and considering a willingness-to-pay threshold of €45,000 per QALY, the vaccine cost

would need to be reduced by 80%, to less than €30 per dose, for HZ vaccination at age 75 and age 80 years to be cost effective. However, at a price of €30.00 per dose, the ICERs for those vaccinated at 50, 55, 60, 65 and 70 years of age inclusive remained above the WTP threshold of €45,000 per QALY. The results of the economic evaluation were robust to probabilistic and one-way sensitivity analysis and various scenario analyses.

The five-year incremental budget impact of an HZ vaccination programme for adults in the general population aged 50 years and older (with 50% coverage), ranged from €15.1 million with vaccination at 85 years old to €76.8 million with vaccination at 50 years old. Offering the vaccine to everyone over a certain age will incur a substantially larger budget impact than a single year of age. For example, if everyone aged 65 years and over was offered the vaccine, with 50% uptake the five-year budget impact would be €218 million. The five-year incremental budget for eligible immunocompromised persons (with 100% coverage) was estimated at €56.2 million. This estimate comprised €46.3 million for the cohort aged 50 years and older with non-specific immunocompromising conditions, €6.3 million for those with haematological malignancies, €2.2 million for solid organ transplant recipients, €745,000 for HSCT recipients and approximately €630,000 for those with advanced/untreated HIV. For all cohorts, the incremental budget impact in year one was significantly greater than years two to five as it was assumed that all those currently eligible for vaccination (the prevalent population) would be vaccinated in year one.

The findings of an economic evaluation are contingent on the quantity and quality of data available to populate the model. Based on extensive scenario and sensitivity analyses, the findings of this evaluation were robust to data and structural assumptions.

7. Organisational issues

The current adult immunisation programme in Ireland funds two annual seasonal vaccines (influenza and COVID-19 booster) as well as their administration, and a pneumococcal vaccine which is typically administered as a once-off. While the pneumococcal vaccine is funded, those without a medical card or GP visit card must pay for the vaccine to be administered, with the individual required to pay the full cost if it is accessed through a pharmacy.

The RZV vaccine is a two-dose vaccine, but can be co-administered with other vaccines in the adult programme. Co-administration of the RZV vaccine with another vaccine in the programme would reduce the overall number of vaccine-related healthcare visits, potentially reducing the burden on patients and healthcare providers. However, co-administration could impact future uptake of the seasonal

vaccines, given the potential for increased side effects with vaccine co-administration. There would likely still be a requirement for an additional visit within the adult programme given the licensed indication to administer both doses of the RZV vaccine within a six-month window. Similar to the existing vaccines in the adult programme, RZV vaccination can be accessed through GP practices and community pharmacies. Over 70% of community pharmacies administer vaccines reimbursed through the HSE programmes.

A decision to fund the RZV vaccine as part of the adult programme could have significant financial and logistical implications depending on the population group for whom the vaccine is funded. For example, a staggered roll-out approach to RZV vaccination would be required if RZV vaccination was extended to all individuals included in the recommendations from the National Immunisation Advisory Committee (approximately 850,000 individuals in the first year and 53,000 each year after that).

There is uncertainty surrounding the potential uptake of the vaccine given the wide range of uptake estimates for other vaccines in the adult immunisation programme and for RZV uptake internationally. For those who do not hold medical cards or GP visit cards, uptake may be lower if the cost of administering the vaccine is passed on to the patient as is currently the case with the pneumococcal vaccine.

An information campaign would be needed to clearly indicate who is eligible for the vaccine and how to avail of it through the adult immunisation programme. For immunocompromised adults aged 18 and older, this may include engagement with clinical specialists in tertiary services to support uptake in identified subgroups. Consideration would also be required regarding the additional steps to track and contact people about their second dose given the two-dose schedule. If a decision were made to fund RZV, consideration would need to be given to defining priority groups for vaccination in the event that demand exceeds supply.

8. Ethical and social considerations

The purpose of vaccination is to prevent or reduce the spread of infectious disease. In terms of the benefit-harm balance, there is clear and consistent evidence that HZ vaccination is effective at reducing incidence of HZ. The evidence suggests that RZV vaccination is safe. While mild local and systemic reactions, such as pain at injection site, fatigue and myalgia, are common, serious adverse events are rare.

Policy makers have a duty to ensure equitable allocation of resources. Reallocation of resources has the potential to affect the existing healthcare system as it may divert resources from other effective treatments provided within the overarching healthcare budget. The introduction of HZ vaccination would create demand for

primary care resources, potentially displacing care. However, this shift could transition the demand from treatment-focused care to a more preventive care-oriented approach.

In terms of respect for autonomy, in the context of HZ, vaccination entails providing individuals with clear and comprehensive information about the vaccine's implications, both for receiving and abstaining, including an understanding of associated risks, while also ensuring healthcare professionals can seamlessly integrate vaccination activities into their daily workflows without compromising care quality.

Evidence from this HTA highlights that, based on current data, vaccinating adults in the general population over the age of 50 years against HZ is not cost effective and is associated with a substantial budget impact. The healthcare budget is finite; including HZ vaccination in the adult immunisation programme could require reallocation of resources, potentially impacting the existing healthcare system by diverting resources from other more cost-effective interventions or from the overall healthcare fund. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity costs (the value of the next best alternative forgone) of new investments are considered. This may prove difficult as there may be many competing claims requiring prioritisation of care. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens. The timing of the assessment impacts on the available data to evaluate the long-term clinical effectiveness of HZ vaccination. There is currently no long-term real-world effectiveness data on waning beyond a four-year timeframe. It is important to offer individuals transparent and accurate information about the limited long-term effectiveness data as part of the informed consent process.

9. Conclusions

In excess of 90% of the population contract varicella and are therefore susceptible to reactivation of the virus as herpes zoster. Approximately 30% of people who have had varicella will go on to have HZ.

The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to persistent chronic pain after the resolution of the acute rash. PHN can significantly alter individuals' lives, inflicting debilitating pain, disrupting daily activities, sleep, and emotional wellbeing. The probability of PHN increases with age, increasing from a one in 10 chance in 50- to 59-year-olds to one in five in those aged over 80 years. Both the risk of HZ and complications from HZ increase with age after 50 years and among individuals who are immunocompromised due to immunosuppressive conditions or therapies.

There is clear and consistent evidence that the recombinant adjuvanted vaccine (RZV) vaccine is safe and effective at reducing HZ cases, but effectiveness diminishes over time. While associated adverse events are typically not severe, most people who are vaccinated will experience minor local or systemic adverse events.

As most people have a short-course of symptoms, and will not be hospitalised, the financial impact of treating HZ is not substantial. At the submitted price, the current evidence suggests that HZ vaccination does not represent an efficient use of healthcare resources. The results of the economic evaluation show that an RZV vaccination programme would fall considerably outside typically accepted willingness-to-pay thresholds. The findings of the cost-effectiveness analysis for the general adult population were robust to sensitivity and scenario analyses. While those with immunocompromising conditions are more likely to develop HZ, and therefore are more likely to benefit from vaccination, the cost effectiveness of vaccination of this group could not be assessed due to limited data availability. Considering a vaccine uptake of 50%, the five-year incremental budget impact of a HZ vaccination programme for adults in the general population as they turn 65 years old (no catch-up for older adults) would be €53.3 million. For all adults aged 65 years and older, the five-year incremental budget impact would be €218 million. The five-year incremental budget for eligible immunocompromised persons (with 100% coverage) was estimated at €56.2 million.

A decision to fund the RZV vaccine as part of the adult immunisation programme could have significant financial and logistical implications depending on the population groups for whom the vaccine is funded. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens.

Plain language summary

Shingles is a viral infection caused by the same virus that causes chickenpox. You can only get shingles if you have already had chickenpox. Three out of every 10 people who have had chickenpox will go on to have shingles at some point in their life. You cannot pass shingles to another person, but coming in contact with shingles can cause chickenpox in someone who has never had it before. Shingles causes a painful, blister-like rash. While the symptoms normally clear up within a month, some people may continue to experience pain for months, or even years after the rash heals. Older people and people with a medical condition or taking a medicine that can weaken their immune system (immunocompromised) have a higher risk of getting shingles.

Shingles vaccines are available in Ireland, but the Health Service Executive (HSE) does not currently provide free vaccination — people must pay to be vaccinated. The vaccines are designed to prevent shingles and its complications in adults. This assessment looked at a two-dose vaccine.

The Department of Health asked the Health Information and Quality Authority (HIQA) to undertake a health technology assessment (HTA) in relation to shingles vaccination. The assessment has been provided as advice to the Minister for Health to help inform a decision on whether this vaccine should be included in the national immunisation programme for adults. As part of this assessment, HIQA has reviewed the available evidence, and has sought input from a group of experts, including public representatives. It also considered the organisational, ethical and social impact of funding the shingles vaccine.

HIQA found good evidence that the shingles vaccine is safe and effective for the general population aged 50 years and older and for immunocompromised adults aged 18 years and older. Although effective when you first receive it, the benefit of the vaccine decreases over time. Serious harms are rare. However, minor reactions are common. These include pain where the injection was given, tiredness, and muscle pain. These reactions are mild and usually resolve within one to two days.

HIQA looked at the impact of adding the shingles vaccine to the adult vaccination programme. At the current vaccine price, it found that adding shingles vaccination to the routine immunisation schedule for all adults aged 65 years and over would not be an efficient use of resources. Offering the vaccine would also cost a lot of money even after considering savings because fewer people go to the GP or are admitted to hospital. For example, if the vaccine was offered to everyone aged 65 years and over and half of people took up this offer, it would cost the HSE an extra €218 million over the first five years. If the vaccine was offered just to those turning age

65 years old and half of people took up this offer, it would cost the HSE an extra €53.3 million over the first five years.

Adults currently receive their vaccines from either their GP or at the pharmacy. One of the main challenges with providing a shingles vaccination programme would be making sure that enough trained people are available to administer another vaccine. It would be important to provide an information campaign for adults as they make the decision on whether they should receive the vaccine. This campaign should include information about the potential complications from shingles and address concerns they may have regarding the safety and effectiveness of the shingles vaccine.

People who develop shingles can suffer from long-term pain and complications. A vaccine is available that is safe and effective, but the benefit of the vaccine decreases over time. At the current vaccine price, we found that adding shingles vaccination to the routine immunisation schedule for all adults aged 65 years and over would not be an efficient use of resources. While making the vaccine available to all would remove an imbalance in fair access to the vaccine, this could create unfairness in other ways. The health service needs to aim for a fair distribution of benefits and burdens for the whole population of Ireland.

List of abbreviations used in this report

ACER	average cost-effectiveness ratio
ADL	activities of daily living
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
BIA	Budget-impact analysis
CDC	Centers for Disease Control and Prevention
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CSO	Central Statistics Office
CUA	cost-utility analysis
DRGs	Diagnostic-Related Groups
ED	Emergency Department
EEA	European Economic Area
EMA	European Medicines Agency
EQ-5D	Euro-QoL five-dimension scale
EU	European Union
GP	General Practitioner
HCW	healthcare workers
HIPE	Hospital Inpatient Enquiry
HSCT	haematopoietic stem cell transplant
HSE	Health Service Executive
HIV	Human Immunodeficiency Virus
HPRA	Health Products Regulatory Authority
HPSC	Health Protection Surveillance Centre
HTA	Health Technology Assessment
HZ	herpes zoster
HZO	herpes zoster ophthalmicus
ICER	incremental cost-effectiveness ratio
IRR	incidence rate ratio
IQR	interquartile range

MMP	Medicine Management Programme
NITAG	Global National Immunization Technical Advisory Groups
NIAC	National Immunisation Advisory Committee
NIO	National Immunisation Office
OR	odds ratio
PHN	post-herpetic neuralgia
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RZV	recombinant zoster vaccine
SAE	serious adverse event
SOT	solid organ transplant
VAT	Value Added Tax
VZV	varicella zoster virus
WHO	World Health Organization
WTP	willingness-to-pay
ZVL	live attenuated zoster vaccine

1 Introduction

1.1 Background to the request

Herpes zoster (HZ), which is commonly known as shingles, is typically recognised by a painful blistering rash on the torso. HZ is caused by reactivation of the varicella zoster virus. Primary infection with the varicella zoster virus results in varicella (commonly known as chicken pox) which typically presents in children. After varicella infections resolve, the virus remains and becomes latent in the body's nervous system. The virus may reactivate after a period of time, typically several decades later, resulting in HZ. HZ can occur at any age, with a lifetime risk of HZ of approximately 30% in those who have previously had varicella.[1] Factors associated with an increased risk of HZ include increasing age and immunocompromised status.[2]

HZ disease is characterised by a vesicular skin rash, often associated with acute pain and itching lasting between two to four weeks.[3, 4] Other symptoms may include headache, myalgia, malaise, and photophobia, which typically lasts for two to three days.[5] Complications of HZ disease are extensive and can contribute considerably to morbidity and mortality risk. The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to the persistence of chronic pain after the resolution of the acute cutaneous HZ lesions. Up to 30% of individuals with HZ will develop PHN.[6] Other complications can include herpes zoster ophthalmicus (HZO), herpes zoster oticus, recurrent or disseminated HZ lesions, as well as neurological and cardiac complications.[3] Immunocompromised individuals are at increased risk of atypical presentations of HZ which may involve a prolonged and or complicated course of disease.[7] In addition to the direct health-related burden experienced by patients, HZ and its complications, such as PHN, can contribute to significant healthcare costs and resource utilisation as well as indirect costs such as lost work time.

As of January 2024, there are two HZ vaccines licensed and marketed in Ireland: a live attenuated virus vaccine (ZVL) (Zostavax®) and a recombinant adjuvanted sub unit vaccine (RZV) (Shingrix®). Agreed updates to guidance from the National Immunisation Advisory Committee (NIAC) recommend HZ vaccination at 65 years and over, due to the greater burden and severity of disease and PHN in this age group.[8] Additionally, the updates recommend RZV be considered in those aged 18 years and older at increased risk of herpes zoster, with the following subgroups noted: adults aged 50 years and over with immunocompromising conditions; HSCT recipients aged 18 years and over; solid organ transplant recipients aged 18 to 49 years; those with haematological malignancies aged 18 to 49 years; and those with uncontrolled HIV aged 18 to 49 years.[9] Currently, these vaccines are not

reimbursed as part of the HSE national immunisation programme. In order to inform a decision as to whether the HZ vaccine should be reimbursed, the Department of Health requested that HIQA complete a health technology assessment (HTA) of universal vaccination with an HZ vaccine as part of the adult immunisation programme.

1.2 Terms of reference

The purpose of the HTA was to provide advice to the Minister for Health to inform a decision on the inclusion of HZ vaccination in the adult immunisation programme in Ireland. In consultation with the Department of Health, HIQA's Evaluation Team developed a set of objectives with consideration to the evidence needs of the decision-maker.

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

- describe the vaccines approved 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 and over and adults 18 years and older who are at greater 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 programme in Ireland
- consider any potential organisational and resource implications of including herpes zoster vaccination in the adult immunisation programme
- consider any ethical and social implications that adding herpes zoster vaccination to the adult immunisation programme may have for patients, the general public or the healthcare system in Ireland
- based on the evidence in this assessment, provide advice to support a decision on whether to include herpes zoster vaccination in the adult immunisation programme in Ireland.

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 patients, 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 Minister for Health
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to HIQA regarding the scope of the analysis
- support the Evaluation Team led by HIQA during the assessment process by providing expert opinion and access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the evaluation team and recommend amendments, as appropriate
- contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

The terms of reference of the HTA were reviewed by the EAG at its first meeting. The protocol, draft chapters on the description of the technology, epidemiology and burden of disease, effectiveness and safety of herpes zoster vaccination strategies, and the review of economic evaluations were circulated to the EAG and discussed at that meeting. Considerations regarding the other domains of the HTA were

discussed at the second meeting of the group. Draft versions of the completed report were circulated for review by the EAG and amended, as appropriate, before a final draft report was prepared for public consultation.

The draft report was published on the HIQA website for targeted and public consultation. The consultation period ran from 19 March 2024 to 30 April 2024. Based on submissions received during the consultation process, further revisions were incorporated into the report, where appropriate. Overall, 96 unique and complete submissions were received; a number of revisions were made to the draft report arising from these submissions. Details of the consultation are provided in the attached statement of outcomes report.

Following completion of the public consultation, a final draft version of the report and the advice to the Minister for Health was circulated to the EAG for review. A revised draft was submitted to the Board of HIQA for approval. Following its approval, the completed assessment is submitted to the Minister for Health and the Department of Health as advice, and published on the HIQA website.

2 Description of the technology

Key points

- There are two vaccines licensed in Europe for the prevention of herpes zoster (HZ) and its most common complication, post-herpetic neuralgia: a live attenuated vaccine (ZVL) and a recombinant adjuvanted vaccine (RZV). The vaccines are authorised for use in adults aged 50 years and older while RZV is additionally authorised for use in adults aged 18 years and older at increased risk of HZ.
- While both vaccines are licensed and marketed in Ireland, neither is currently funded by the HSE.
- 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, the company has made the decision to voluntarily discontinue manufacturing and supplying ZVL. The proposed date for discontinuation is 31 July 2024. As such, ZVL was not formally assessed in this HTA.
- Internationally, there are differences among immunisation programmes against HZ with respect to the type of vaccine, level of public funding, the age group(s) eligible to be vaccinated, and the vaccination of individuals at increased risk of HZ. As of January 2024:
    - HZ vaccination is recommended and publicly funded for the general population in five countries in the EU and partially funded in one. Beyond countries in the EU/EEA, Australia, New Zealand, Switzerland, and the United Kingdom (UK) also fund the vaccine within their national immunisation programmes, and funding is state-/province-dependent in the USA and Canada, respectively.
    - The age at which adults in the general population are eligible for HZ vaccination is 65 years or older in the majority of these countries.
    - For those at increased risk of HZ, vaccination is variably offered from age 18 years or from age 50 years, with a number of countries specifying that funding is limited to those who are severely immunosuppressed or identifying the categories of patients for whom vaccination is funded.

2.1 Introduction

The purpose of this chapter is to describe the two herpes zoster (HZ) vaccines licensed in Europe that protect against re-activation of latent varicella zoster virus (VZV) in adults and subsequent HZ disease (shingles) and related complications. This chapter also provides background on VZV's potential as a pathogen and the resulting disease, which will be explored in greater detail in Chapter 3. A description of current international HZ vaccination programmes for adults in place in Europe and a select number of other countries is provided, which was informed by a scoping review. In addition, the current adult immunisation programme in Ireland is described. Lastly, a brief overview of the management of HZ is provided, which will be described in more detail in Chapter 3.

2.2 Herpes zoster disease and detection of varicella zoster virus

VZV is a double-stranded DNA virus and one of eight herpesviruses known to routinely infect humans only.[10] All eight herpesviruses can establish latent infection in specific tissues. They can be divided into three groups — alpha, beta and gamma — based on their replicative cycle and host range.[10] VZV is one of three alpha herpesviruses (including herpes simplex virus 1 and 2),[10] which are human neurotropic viruses, meaning they can infect nerve cells and cause neurological manifestations.[11]

VZV is usually transmitted by inhalation of respiratory droplets, by direct contact with vesicular fluid, or by contact with fomites.[4] It enters the host through the respiratory tract or conjunctiva, replicating at the point of entry in the nasopharynx and in regional lymph nodes.[12] Primary infection with VZV results in varicella, a common, highly infectious disease mainly affecting children.[3] Although typically a mild disease, serious complications requiring hospitalisation occur in approximately one in 250 cases. Varicella can also lead to long-term skin scarring.[13]

Following primary infection, the virus subsequently becomes latent in the cells of the dorsal root or cranial nerve ganglia. After a period of time (up to several decades) the virus may reactivate, resulting in HZ.[3] Only individuals who have previously been infected with VZV are at risk of developing HZ,[14] with these individuals having an approximately 30% lifetime risk of developing HZ.[6, 15] Serology can indicate historical varicella infection and demonstrate prior exposure to VZV.[4]

The disease is characterised by a vesicular rash localised in the sensory region of the affected ganglia, often associated with acute pain and itching. In immunocompetent individuals, the rash typically manifests in one or two thoracic dermatomes of the torso, and usually does not cross the midline as the virus is localised to specific

ganglia.[7] Immunocompromised individuals are at increased risk of additional atypical presentations of HZ which can include prolonged course of disease, recurrent HZ lesions, multiple dermatome involvement and lesions with chronic crusts or verrucous nodules.[7]

Zoster-associated pain can be classified into three types based on duration: the acute phase (including the initial prodromal phase and up to 30 days after infection); the subacute phase (persistent for 30 to 90 days); and post-herpetic neuralgia (PHN), typically defined as pain persisting more than 90 days following onset of rash. PHN can result in severe, incapacitating pain that can persist for a period of months to years.[3]

Typically, diagnosis of HZ disease is primarily clinical, because of the characteristically localised rash.[4] Clinical diagnosis may also be informed by the presence of prodromal or acute pain.[3] In cases where there is diagnostic uncertainty due to atypical presentation, such as the disseminated zoster rash that can occur more frequently in immunocompromised individuals, diagnosis can be confirmed through laboratory testing of a swab or cell scraping from the base of the lesions or vesicular fluid.[16] Confirmation can be made via direct fluorescent antibody staining, cell culture, or polymerase chain reaction.[3, 16]

2.3 Vaccines

2.3.1 Vaccine description

There are two HZ vaccines licensed and marketed in Ireland — a live attenuated varicella zoster vaccine (ZVL) and a recombinant zoster vaccine (RZV).[17, 18] These vaccines are not currently funded by the HSE. The key characteristics of each vaccine are summarised in Table 2.1

Zostavax® (Merck Sharp & Dohme BV) is a live attenuated varicella zoster vaccine produced in human diploid cells. It received marketing authorisation from the European Medicines Agency (EMA) in 2006. Zostavax® is administered as a single dose and is indicated for the prevention of HZ and associated PHN in adults aged 50 years or older. The use of Zostavax® is contraindicated in individuals with primary and acquired immunodeficiency states and in those receiving immunosuppressive therapy (including high-dose corticosteroids). It is not recommended to use Zostavax® in children or adolescents for prevention of primary varicella infection. 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, the company had made the decision to voluntarily discontinue manufacturing and supplying Zostavax®; the proposed date for discontinuation is 31 July 2024.[19] This decision by the manufacturer is not due to any product safety or quality issue.[19] As

such, while currently still available for use, it is not relevant to a prospective change to the HSE immunisation programme. Information on Zostavax® is therefore only presented for context and the vaccine will not be formally assessed in this HTA.

Shingrix® (GlaxoSmithKline (GSK) Biologicals SA) is a recombinant adjuvanted sub unit vaccine that contains a protein (glycoprotein E) from VZV. It received marketing authorisation from the EMA in 2018. Shingrix® is administered as a two-dose vaccine for the prevention of HZ and associated PHN in adults aged 50 years or older. In 2020, marketing authorisation was also approved for adults aged 18 or older who are at increased risk of HZ. Those considered at increased risk of HZ are discussed in detail in Chapter 3. The second dose is administered between two and six months after the first dose; however, the interval can be reduced to one month if deemed necessary for individuals who are or might become immunocompromised or immunosuppressed. Shingrix® contains VZV specific antigen (glycoprotein E) with an adjuvant system ($AS01_B$) to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV. Thus, Shingrix® is not indicated for prevention of primary varicella infection. Shingrix® can be administered to individuals who have previously received a live attenuated HZV.

For both vaccines, it is important to ensure that individuals do not have hypersensitivity to the active substances or any excipients. For Zostavax®, there are several additional contraindications, as outlined in Table 2.1

2.3.2 Co-administration with other vaccines

Based on the Summary of Product Characteristics, the following points are noted with regard to co-administration of the two licensed vaccines against HZ with other vaccines:

- Zostavax® can be given concomitantly with inactivated influenza vaccine as separate injections and at different body sites.[20]
- Zostavax® can be co-administered with coronavirus disease 2019 (COVID-19) vaccines.
- Concomitant use of Zostavax® and 23-valent pneumococcal polysaccharide vaccine resulted in reduced immunogenicity of Zostavax® in a small clinical trial. Data from a large observational study did not indicate risk for developing HZ after concomitant administration of the two vaccines, however.[20]
- Shingrix® can be given concomitantly with unadjuvanted inactivated seasonal influenza vaccine, PPV23, 13-valent pneumococcal conjugate vaccine (PCV13) or reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTap) or COVID-19 messenger ribonucleic acid (mRNA) vaccine. The vaccines should be administered at different injection sites.[21]

- Concomitant use of Shingrix® with other vaccines is not recommended due to a lack of data.[21]

In addition, according to the National Immunisation Advisory Committee (NIAC) Immunisation Guidelines, there should be an interval of at least seven days between giving an individual a COVID-19 vaccine and Zostavax®.[4]

Table 2.1 Summary of key characteristics of the authorised herpes zoster vaccines marketed in Ireland

Trade name	Zostavax®(20)	Shingrix®(21)
Type of vaccine	Live, attenuated	Recombinant, adjuvanted
Manufacturer	Merck Sharp & Dohme BV	GlaxoSmithKline (GSK) Biologicals SA
Marketing authorisation	EMA authorisation: 19/05/2006	EMA authorisation: 21/03/2018
Vaccination schedule	Single dose of 0.65mL	Two doses of 0.5 mL each, an initial dose followed by a second dose administered two months later. If flexibility in the vaccination schedule is necessary, the second dose can be given between two and six months after the first dose. For individuals who are or might become immunodeficient or immunosuppressed, the second dose can be given one to two months after the initial dose (if deemed beneficial).
Formulation	One dose (0.65 mL) contains: ▪ Varicella-zoster virus[1], Oka/Merck strain, (live, attenuated) not less than 19,400 PFU [1] produced in human diploid (MRC-5) cells	One dose (0.5 mL) contains: ▪ Varicella zoster virus glycoprotein E antigen[1,2], 50 micrograms [1] adjuvanted with $AS01_B$ containing plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) (50 micrograms) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (50 micrograms) [2] glycoprotein E produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology
Therapeutic indications	Zostavax® is indicated for prevention of herpes zoster (HZ) and herpes zoster-related post-herpetic neuralgia (PHN) in: ▪ adults 50 years of age or older	Shingrix® is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN) in: ▪ adults 50 years of age or older; ▪ adults 18 years of age or older at increased risk of HZ.
Contraindications	▪ Hypersensitivity to the active substance, any excipients, or neomycin (trace residues). ▪ Primary and acquired immunodeficiency states due to conditions such as: acute and chronic leukaemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV-AIDS; cellular immune deficiencies.	Hypersensitivity to the active substances or any excipients.

Trade name	Zostavax®[20]	Shingrix®[21]
	▪ Immunosuppressive therapy (including high-dose corticosteroids). However, not contraindicated for use in individuals receiving topical/inhaled corticosteroids, low-dose systemic corticosteroids, or corticosteroids as replacement therapy. ▪ Active untreated tuberculosis. ▪ Pregnancy (avoid pregnancy for one month following vaccination).	

Key: EMA – European Medicines Agency; HIV-AIDS – Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome; MRC-5 – Medical Research Council cell strain 5; PFU – plaque forming units

2.3.3 Administration and manufacturers' stipulated storage

Shingrix® should be injected intramuscularly, preferably in the deltoid muscle. Caution should be exercised when administering to individuals with thrombocytopenia or any coagulation disorder, since bleeding may occur following intramuscular administration to these subjects.[21] The medicinal products constituting the vaccine should be kept refrigerated at temperatures between 2°C and 8°C when being stored and transported, and should not be frozen. Prior to reconstitution the medicinal products have a shelf life of three years under appropriate storage conditions. After reconstitution, from a microbiological perspective, the vaccine should be used immediately, but if not used immediately should be used within six hours, having been stored between 2°C and 8°C. However, chemical and physical stability has been demonstrated for up to 24 hours at 30°C. The user retains responsibility for the appropriate storage and use of the vaccine after reconstitution.

Zostavax® vaccine can be injected under the skin (subcutaneously) or intramuscularly, preferably in the shoulder (deltoid) region. Prior to reconstitution it has a shelf life of 18 months under appropriate storage conditions. After reconstitution, the vaccine should be used immediately, but can be considered stable to use for up to 30 minutes when stored at temperatures between 20°C and 25°C.[20]

2.4 Current use of vaccine

2.4.1 HZ vaccination in Ireland

HZ vaccination is currently not included in the publicly funded adult national immunisation programme in Ireland. However, both vaccines are authorised for use in Ireland and can be purchased privately through consultation with a GP or pharmacist. HZ vaccines are recommended by the National Immunisation Advisory Committee (NIAC) for the prevention of HZ and associated PHN in adults aged 50 years or older, with RZV also recommended in adults aged 18 years or older at an increased risk of HZ. For both vaccines it is advised to defer vaccination during pregnancy. Additional contraindications associated with the ZVL vaccine are summarised in Table 2.1

2.4.2 HZ vaccination internationally

To provide an overview of current international practice regarding HZ vaccination programmes, a scoping search was performed to examine recently published academic literature and HTA outputs (searched using PubMed Clinical Queries Tool, Google Scholar for forward citation searching, the International Network of Agencies for Health Technology Assessment (INAHTA) database, and the Global National

Immunization Technical Advisory Groups (NITAG) Network resource). This was supplemented with a targeted grey literature search of public health organisations and websites of governmental departments of countries identified in the literature and deemed to be of most relevance to Ireland, to check for recent updates to their vaccination policy. Additionally, this list of countries was informed by those countries identified as having childhood varicella vaccination programmes in place as part of a previous HTA.[13] These comprised countries in the European Economic Area (EEA), Switzerland, Canada, the United States, the United Kingdom, Australia, and New Zealand. The information presented is current up to 8 January 2024.

A summary of findings of this review is presented in Table 2.2. The vaccination programmes against HZ differ from country to country, with respect to the choice of vaccine, the age group(s) eligible to be vaccinated, level of public funding, and the decision to vaccinate individuals at increased risk due to underlying conditions or immunocompromised health status. A decision to provide public funding may have been conditional on confidential price reductions from the manufacturer. As such, the programmes may also differ in the negotiated vaccine prices.[22]

Vaccination of general population

Five EU/EEA countries were identified as funding vaccination against HZ within their national immunisation programme for adults in the general population (Germany, Greece, Italy, Luxembourg and Spain). In addition, HZ vaccination is partially funded in France, and recommended, but not funded, in Austria and the Czech Republic. Beyond countries in the EU/EEA, Australia, New Zealand, Switzerland, and the United Kingdom (UK) also fund the vaccine within their national immunisation programmes (Table 2.2).

In the USA, the Centers for Disease Control and Prevention recommends HZ vaccination for adults aged 50 years and older and adults aged 19 years and older who have weakened immune systems because of disease or therapy. Funding and insurance coverage in the USA is insurer- and state-dependent for the recommended age groups.[23] In Canada, HZ vaccination is recommended at a national level, but only publicly funded by the immunisation programmes in four provinces (Ontario, Prince Edward Island, Yukon and Quebec) (Table 2.2).

Vaccination of adults at increased risk of HZ

In addition to vaccinating adults in the general public, several countries also recommend vaccination of individuals at increased risk of HZ due to underlying conditions or immune suppression, or based on their race or ethnicity (Table 2.2). Three countries (Germany, Switzerland and UK) fund vaccination of adults aged 50 years and older who are considered immunocompromised. In Poland there is partial

(50%) reimbursement of RZV for individuals aged 65 years and older who are at higher risk of HZ disease and complications.[24] Italy funds HZ vaccination of adults aged 50 years and older with underlying conditions. Since 2023, Italy also funds HZ vaccination for individuals from 18 years of age for those with immunodeficiency or requiring immunosuppressive therapy, as well as for individuals with chronic renal failure, those requiring dialysis, and those experiencing relapse or severe shingles.[25] Six other countries (Australia, Luxembourg, The Netherlands, Spain, Slovenia and Belgium) and two Canadian provinces (Yukon, Quebec) recommend and fund vaccination of adults considered immunocompromised from age 18 years. The Netherlands, Australia and Spain define this cohort as stem cell transplant patients, solid organ transplant patients, patients with advanced or untreated HIV, and haematological malignancies.[26-28] Spain additionally recommends vaccination for patients with solid tumours undergoing chemotherapy and patients receiving treatment with JAK inhibitors. Three additional countries fund vaccination from 18 years for specific groups: those with severe immunocompromised status including patients with haematological malignancies, stem cell and solid organ transplant recipients, HIV-positive patients with less than 200 CD4 T cells per microliter, persons treated with JAK inhibitors or intensive immunosuppression due to an immune-mediated disease such as rheumatoid arthritis or inflammatory bowel disease (Switzerland);[29] those experiencing recurrent cases of HZ (Greece);[30] those who have received a stem cell transplant (Scotland).[31] Vaccination of individuals considered immunocompromised is recommended, but not directly funded, by the Czech Republic, New Zealand and USA. Finally, Australia funds vaccination for Aboriginal and Torres Strait Islander individuals aged 50 years and over. (Table 2.2).

Summary of country level information

Specific reference to the rationale and evidence underpinning the decision to fund HZ vaccination as part of the national immunisation programme was identified for six countries (Spain, France, Luxembourg, Germany, the UK and Australia). For five national programmes, the decision on which vaccine to use and the age cohort to vaccinate was influenced by the findings of cost-effectiveness analyses. In Spain in 2017, the Ministry of Health commissioned a cost-effectiveness study comparing ZVL, RZV and no vaccination. Vaccinating those aged 65 years with RZV was associated with a cost per quality-adjusted life year (QALY) gained of €6,930 compared with not vaccinating and this strategy was more effective and less costly compared with vaccinating with ZVL.[27] Vaccination of immunocompromised individuals was considered cost effective, compared with not vaccinating, at a cost per QALY gained of €4,468. In France in 2013, the Haut Conseil de la Santé Publique (HCSP) carried out a cost-effectiveness analysis to determine the most cost effective strategy for vaccinating immunocompetent adults aged 60 years and older. Informed

by this analysis, the HCSP recommended vaccination of adults from 65 to 74 years with ZVL.[32] In December 2022, Haute Autorité de Santé in France published a framework outlining an objective to develop updated guidelines for vaccination against HZ and taking into account the availability of the RZV® vaccine, with potential to inform the 2024 vaccination schedule.[32] In Germany in 2019, a cost-effectiveness analysis informed the decision to vaccinate with RZV at age 60 years, as it was noted that most cases of HZ would be prevented under this scenario.[33] In the UK, the original recommendation by the Joint Committee on Vaccination and Immunisation (JCVI) to vaccinate individuals aged 70 years was informed by a 2009 cost-effectiveness analysis that found that vaccination at either 65 or 70 years of age was likely to be most cost effective.[34] In 2019, informed by cost-effectiveness modelling, the JCVI recommended that the vaccination programme against HZ be changed, with RZV offered routinely at the age of 60 years.[35] For Luxembourg, the 2022 recommendations in favour of HZ vaccination with RZV from the Conseil Supérieur des Maladies Infectieuses (CSMI) refer to an increase in scientific evidence in support of vaccination, especially for immunocompromised individuals, and the positive consequences of vaccination, such as a reduced burden on the health system.[36] In Australia in July 2023, while noting the cost of the programme was high, the Pharmaceutical Benefit Advisory Committee (PBAC) recommended funding RZV for adults aged 65 years (primary programme) and older (catch-up programme).[22] Based on a reduced price proposed by the manufacturer, PBAC considered that RZV was cost effective for this cohort, with no upper age limit for a catch-up programme. The PBAC noted the cost effectiveness of RZV relies on accepting the long term modelled vaccine efficacy, and in this context considered that the cost effectiveness of RZV should be reassessed if a booster dose is required or if long-term efficacy is less than predicted. RZV was listed on the Australian immunisation programme in November 2023 for non-Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged 50 years and older and immunocompromised individuals aged 18 years and older.

In summary, of the countries and regions identified that reimburse HZ vaccination, only three countries currently fund vaccination with the ZVL. However, one of these three countries (France) is currently reviewing their guidelines for vaccination against HZ taking into account the availability of the RZV vaccine. The remaining countries with national immunisation programmes against HZ have updated their guidelines to provide vaccination with the RZV vaccine.

As noted in section 2.2, primary infection with varicella zoster virus results in varicella, a common, highly infectious disease mainly affecting children.[3] There are currently four varicella vaccines authorised for vaccination against varicella by either the Health Products Regulatory Authority in Ireland or the EMA.[13] All four are live attenuated vaccines, two monovalent (varicella only) and two quadrivalent

(combined measles, mumps, rubella and varicella (MMRV)) vaccines. Information on international varicella vaccination programmes for children was gathered as part of an HTA published by HIQA in July 2023 and is included for convenience in Table 2.2.[13]

Table 2.2 Overview of international HZ vaccination programmes

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
Australia[22, 28] **Nov, 2023**	Since November 2023, national recommendations align with funded National Immunisation Programme.[28]	RZV was added to the National Immunisation Programme in November 2023 for:[22, 28] ▪ non-Indigenous individuals aged 70 years ▪ Aboriginal and Torres Strait Islander individuals aged 50 years and over ▪ immunocompromised individuals aged 18 years and over with conditions considered at high risk of HZ infection.	Recommended and funded.[37]
Austria[38-40] **Jan, 2022**	Vaccination with RZV is recommended, but not funded for:[38-40] ▪ Adults aged 50 years and over, subject to a fee ▪ Certain groups of adults (severe underlying disease and/or severe immunosuppression) aged 18 years and older.	RZV has been available at a cost to the individual in Austria since 2021.[38, 39] Vaccination against HZ is subject to a fee.[39, 40]	Recommended but not funded.[41]
Belgium[42] **Nov, 2023**	Vaccination is recommended for adults ages 60 years and older and immunocompromised individuals under immunosuppressive therapy aged 16 years and older and also patients under treatment with anti-JAK therapy.[43]	RSV is reimbursed for individuals aged 18 years or older if they have a haematological malignancy or a malignant tumour and have been actively treated within the past 5 years, have HIV infection, or have received organ or HSCT or are eligible for a transplant.[42]	Selected recommendation and funding for people who are in close contact with someone who is particularly vulnerable to chickenpox or its complications.[44]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
Canada[45, 46] **Oct, 2023**	RZV is recommended for immunocompetent adults aged 50 years and over.[45] RZV is recommended for adults aged 18 years and older at increased risk of HZ. Recommendation under review by the National Advisory Committee on Immunization due to changes in the Summary of Product Characteristics.[45]	RZV was authorised in 2017 and included in updated recommendations by the National Advisory Committee on Immunization in 2018.[46] Provinces and territories determine their vaccination schedule for their region.[45]	Recommended and funded.[47]
Provinces/Territory[48] **Alberta** **Manitoba** **New Brunswick** **Newfoundland and Labrador** **Nova Scotia** **Nunavut** **Saskatchewan**	As per national recommendations above.	HZ vaccination not included in funded vaccination schedule.	
Province/Territory[48] **British Columbia** **Northwest Territories**	HZ vaccine recommended for adults aged 50 years and older, at a cost to the individual.	HZ vaccination not included in funded vaccination schedule.	
Ontario[49] **June, 2022**	As per national recommendations above.	RZV added to funded vaccination schedule in 2020. Adults aged 65 to 70 years, two doses two to six months apart. Two-dose series should be completed prior to 71st birthday.	
Prince Edward Island[50] **Dec, 2023**	As per national recommendations above.	RZV added to funded vaccination schedule in 2022 for adults aged 60 years and older.	
Yukon[51] **Nov, 2021**	As per national recommendations above.	RZV added to funded vaccination schedule in 2021. From 2023 available	

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
		for adults aged 65 years to 79 years (Yukon residents). Adults aged 18 years and older who are considered immunocompromised may be eligible.	
Quebec[52] **May, 2023**	Recommended for adults aged 50 to 79 years at a cost to the individual.	From May 2023, RZV is available free of charge for adults aged 80 years and older and for adults aged 18 years and older who are considered immunocompromised.	
Czech Republic[53] **Sept, 2023**	In September 2023, the Czech Vaccinological Society recommended using RZV and no longer recommended using ZVL.[53] RZV is recommended for:[53] ▪ adults aged 50 years and older ▪ adults aged 18 years and older who are considered immunocompromised.	Not funded.[54]	Recommended for particular groups and not funded.[41]
Finland[55, 56] **July, 2023**	No recommendation. The shingles vaccine is not part of the national vaccination programme, but is available at a cost to the individual.[55]	Not funded.	Recommended and funded.[41]
France[32, 57] **Sept, 2023**	Recommended for adults aged 50 years and older.[32, 57] *	Since 2015, vaccination with ZVL covered at 30% for adults aged between 65 years and 74 years. Not reimbursed by health insurance outside this age group.[32, 57]	No recommendation.[58]
Germany[59] **Jan, 2023**	National recommendation aligns with funded vaccination strategy.[59]	Vaccination with RZV recommended and funded since December 2018.[60] Standard vaccination as part of national immunisation schedule for adults aged 60 years and older.[59]	Recommended and funded.[41]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
		Indicated vaccination for risk groups: adults aged 50 years and older with an increased risk of HZ (underlying disease or immunosuppression).[59]	
Greece[30] **July 2023**	National recommendation aligns with funded vaccination strategy.	ZVL was added to vaccination schedule in 2011.[61] ZVL recommended for immunocompetent adults aged between 60 and 75 years.[30] In 2023, the national immunisation committee in Greece recommended RZV for adults with immunosuppression aged 60 years and older, and adults aged 18 years or older with recurrent episodes of shingles.[30]	Recommended and funded.[41]
Hungary[62, 63] **August, 2022**	No recommendation.	Not funded.	Mandatory.[41]
Iceland[62, 64] **June, 2023**	No recommendation.	Not funded.	Recommended and funded.[41]
Italy[25] **August, 2023**	National recommendation aligns with funded vaccination strategy.	ZVL was added to the vaccine schedule in 2017.[61] ZVL is recommended for:[65, 66] ▪ adults aged 65 years and older and ▪ adults aged 50 years and older with increased risk due to underlying conditions (diabetes, COPD, cardiovascular disease, prior to immune suppressive therapy). Since 2023, RZV is recommended for:[25]	Mandatory.[41]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
		▪ adults aged 18 years or older with immunodeficiency or requiring immunosuppressive therapy ▪ adults with chronic renal failure and on dialysis ▪ adults with relapses or severe forms of shingles.	
Latvia[61, 67] **Oct, 2023**	No recommendation.	Not funded.	Mandatory.[41]
Luxembourg[36, 68] **April, 2023**	Adults between the ages of 50 and 65 years can be vaccinated, but not for free as part of the national vaccination programme.[68]	From April 2023, RZV was made available free of charge for:[68] ▪ Adults aged 65 years and older ▪ Adults aged 18 years and older who are or will be immunocompromised due to illness or treatment.	Recommended and funded.[41]
The Netherlands[26] **June, 2021**	Adults over the age of 50 years can choose to get vaccinated at their own expense.[26]	From 2021, RZV was recommended only for insured adults aged 18 or over who are immunocompromised due to illness or treatment.[26]	No recommendation.[41]
New Zealand[69, 70] **June, 2023**	Adults aged 50 years and older can choose to get vaccinated at their own expense.[69] Adults aged 18 years and older with increased risk of HZ due to being immunocompromised can get vaccinated at their own expense. [69]	From September 2022, RZV was recommended and funded for:[70] ▪ Adults at age 65 years ▪ Adults aged 65 years who previously received ZVL (with at least one year having passed).	Recommended and funded.[71]
Poland[24] **Jan, 2024**	Individuals aged 65 years and older with increased risk of HZ.[24]	There is partial reimbursement of RZV (50% reimbursement) for individuals aged 65 years and older with increased risk of HZ.[24]	Selected recommendation and funding for people who are particularly vulnerable to chickenpox or its complications. Vaccination is mandatory and funded for individuals at high risk of varicella.[72]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
Slovenia[73] **Autumn, 2023**	Recommend for adults aged 60 years and older and individuals aged 18 years and older at increased risk of HZ. Adults aged 60 years and older can choose to get vaccinated at their own expense.[73]	Funded for those at increased risk aged 18 years and older.[73]	Selected recommendation for people who are particularly vulnerable to chickenpox or its complications.[74]
Spain[75, 76] **Oct, 2023**	National recommendation aligns with funded vaccination strategy.	Phased introduction of RZV vaccine due to limited supply of vaccine:[27] ▪ From 2021, adults aged 18 years and older who are considered immunocompromised ▪ From 2022, expansion of programme to be available for immunocompetent adults aged 65 years. Aim to roll out to all autonomous regions before the end of 2024. Depending on availability of doses, at least one cohort per year will be vaccinated, starting with the cohort turning 80 years and moving down in age until reaching the first cohort vaccinated at age 65 years. ▪ Adults aged 65 years and older who previously received ZVL (with at least five years having passed).	Recommended and funded.[41]
Switzerland **Nov, 2023**[29, 77]	Adults aged between 65 and 79 without immunodeficiency who prefer so may choose ZVL instead of RZV but this will not be reimbursed by health insurance.	Since February 2022, RZV has been recommended and reimbursed by the compulsory health insurance for:[29] ▪ Adults aged 65 years and older ▪ Adults with immunodeficiency aged 50 years and older	Recommended and covered by compulsory health insurance.[29]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
		▪ Adults with severe immunodeficiency aged 18 years and older.	
Sweden[78] **Oct, 2022**	Currently not recommended.	Public Health Agency of Sweden conducting a review regarding inclusion of vaccination against varicella and HZ in national vaccination programmes.	No recommendation.[41]
United Kingdom **England[79]** **Sept, 2023**	Adults aged 50 years and older can privately pay to receive either vaccine, outside of the national programme.[80] [81] Adults aged 18 years and older who are at increased risk can privately pay to receive RZV, outside of the national programme.[80] [81]	From September 2023, RZV is recommended and provided by the national immunisation programme for:[79] ▪ adults in the general population aged 70 to 79 years ▪ adults in the general population turning 65 or 70 from 1 September 2023 (and then adults turning 65 or 70 from 1 September in subsequent years) ▪ adults aged 50 years and older who are severely immunosuppressed.	Selected recommendation and funding for people who are in close contact with someone who is particularly vulnerable to chickenpox or its complications.[82]
United Kingdom **Northern Ireland[83]** **Sept, 2023**	Adults aged 50 years and older can privately pay to receive either vaccine, outside of the national programme.[81] Adults aged 18 years and older who are at increased risk can privately pay to receive RZV, outside of the national programme.[81]	From September 2023, RZV is recommended and provided by the national immunisation programme for:[83] ▪ adults aged 65 on 1 September 2023 and born between 2 September 1957 and 1 September 1958 ▪ adults aged 70 on 1 September 2023 and born between 2 September 1952 and 1 September 1953	Selected recommendation and funding for people who are in close contact with someone who is particularly vulnerable to chickenpox or its complications.[82]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
		▪ adults aged 50 or over on 1 September 2023 considered severely immunocompromised ▪ adults aged between 71 and 79 born between 2 September 1943 and 1 September 1953.	
United Kingdom **Scotland[31]** **Sept, 2023**	Adults aged 50 years and older can privately pay to receive either vaccine, outside of the national programme.[81] Adults aged 18 years and older who are at increased risk can privately pay to receive RZV, outside of the national programme.[81]	From September 2023, RZV is recommended and provided by the national immunisation programme for: [31] ▪ adults aged 65 or 70 (defined by patient's age at 1 September 2023) ▪ adults aged 71 to 79 years (defined by patient's age at 1 September 2023) who have not previously been vaccinated ▪ adults aged 50 years and over considered severely immunocompromised ▪ adults aged 18 and over who have received a stem cell transplant, including recipients of allogeneic transplant, autologous transplant, chimeric antigen receptor T-cell therapy, or similar therapy.	Selected recommendation and funding for people who are in close contact with someone who is particularly vulnerable to chickenpox or its complications.[82]
United Kingdom **Wales[81]** **Sept, 2023**	Adults aged 50 years and older can privately pay to receive either vaccine, outside of the national programme.[81] Adults aged 18 years and older who are at increased risk can privately pay to receive RZV, outside of the national programme.[81]	From September 2023, either vaccine is available as part of the national immunisation programme for: [81] ▪ adults aged 65 years (on or after 1 September 2023) ▪ adults aged 70 to 79 years.	Selected recommendation and funding for people who are in close contact with someone who is particularly vulnerable to chickenpox or its complications.[82]

Country/Province Last update	National recommendation	Funding status	Varicella vaccination programme
		Additionally, from September 2023, RZV is available as part of the national immunisation programme for: ▪ adults aged 50 years and over who are severely immunosuppressed.	
United States of America[23, 84-86] **May, 2023**	From 2018, RZV is recommended for adults aged 50 years and older.[86] From 2021, RZV is recommended for adults aged 19 years and older who are immunocompromised.[86]	Funding dependent on health care cover:[85] ▪ Medicare Part D coverage: free ▪ Medicaid: state dependent ▪ Private health insurance: insurer dependent ▪ Vaccine assistance programmes: manufacturer dependent.	Recommended and funded.[87]

Key: HZ – herpes zoster

Notes: *currently under review in relation to RZV as an alternative to ZVL[32]
This table is limited to countries that have either a HZ or varicella vaccination programme.

2.5 Current adult immunisation programme

The vaccination programmes for vaccines that are routinely offered to adults in Ireland are described in Table 2.3. The HSE funds or partly funds a number of vaccines for the general adult population:

- The flu vaccine is available through the HSE's Seasonal Influenza Vaccination Programme from October to April each year and is currently fully funded for a number of specified occupational groups, for children aged two to 17 years, pregnant women, for identified groups aged from 18 to 64 years at increased risk of severe disease, and for those aged 65 years and older.[88]
- The PPV23 pneumococcal vaccine is available to everybody aged 65 years and over and those aged two years and over at high risk of invasive pneumococcal disease. A once-only booster vaccination is recommended five years after the first vaccination for those who received a previous dose at less than 65 years of age.[89] Of note for PPV23: while the vaccine is free, a consultation fee is charged for those without a GP visit card or medical card. The full cost must be paid by the individual if accessed through a pharmacy.
- COVID-19 booster vaccinations are offered to some adults. The COVID-19 vaccination programme is subject to regular review based on monitoring of the epidemiological situation. In autumn 2023 booster doses were available to those:
  - age 50 and older
  - age five or older with a weak immune system
  - age 5 to 49 with a condition that puts them at high risk of serious illness from COVID-19
  - healthcare workers.[90]

Table 2.3 Reimbursed immunisations for the general adult population*

Vaccine	Target population	Dose and frequency	Location	Cost
Influenza vaccine[88]	Everyone aged 65 years and over.*	One dose annually.	GP and pharmacy.	Free of charge.
PPV23 pneumococcal vaccine[89]	Everyone aged 65 years and over.*	Generally once; but once-only booster vaccination is recommended five years after the first vaccination for those who received a previous dose at less than 65 years of age.	GP and pharmacy.	Vaccine is free, when accessed through the GP, but a consultation fee will be charged for those without a GP card or medical card. The full cost must be paid by the individual if accessed through a pharmacy.[91]
COVID-19 booster vaccine[90]	The COVID-19 vaccination programme is subject to regular review based on monitoring of the epidemiological situation. In autumn 2023, booster doses are available to those age 50 and older.*	As recommended by NIAC.	GP and pharmacy.	Free of charge.

Key: COVID-19 – coronavirus disease 2019; GP – general practitioner; PPV23 – 23-valent pneumococcal polysaccharide vaccine

***Note:** In addition, there are groups of adults that may be eligible for reimbursed vaccination on the basis of their occupation or underlying conditions that put them at increased risk of severe disease.[88-90]

2.6 Management of herpes zoster and its complications

The main aims of treatment for HZ are to decrease pain, induce quick healing, and minimise risk of complications. In the absence of risk factors for complications, HZ is usually a self-limiting disease.[3] The Health Service Executive (HSE) recommends prescribing an oral antiviral within 72 hours of onset of rash in all patients over 50 years of age who develop HZ, in order to reduce the risk of PHN.[92] In addition, the prescribing of oral antiviral is recommended for individuals with complicated disease presentation or who are at increased risk of severe HZ or associated complications. Detailed consideration of treatments for HZ are expanded on in Chapter 3.

2.7 Discussion

Herpes zoster (HZ) is a viral disease that mainly affects adults, with older adults experiencing more severe symptoms. The individual lifetime risk of developing HZ for those who have previously been infected with varicella zoster is approximately 30%. The primary symptom is a painful rash, with long-term pain (post-herpetic neuralgia) a common complication.

There are two vaccines licensed and marketed in Ireland for preventing herpes zoster, the RZV and the ZVL. However, only the manufacturer of RZV intends to continue to market the vaccine in Ireland. Internationally, vaccination programmes against HZ differ from country to country, with respect to the choice of vaccine, the age group(s) eligible to be vaccinated, the decision to vaccinate individuals at increased risk due to underlying conditions or immunocompromised health status, and the cost to the individual.

As of 2023, several countries have recently added, or are in the process of adding, HZ vaccination to their national immunisation programmes. Two of five countries that previously funded the ZVL updated their immunisation programmes in 2023 to include funding for RZV instead; a third country (France) is currently in the process of reviewing their schedule. The remaining countries that include vaccination against HZ in their national immunisation programme fund the RZV.

The age group(s) eligible to be vaccinated within the national immunisation programme varies by country. Considering the general adult population, eight countries and two Canadian provinces fund vaccination in adults aged 65 years (or 65 years and older), two countries fund vaccination from age 60 years and two from age 50 years. Québec funds vaccination for adults aged 80 years and older. Four countries and two Canadian provinces specify an upper age limit for eligibility within their programme.

For individuals at increased risk of HZ, immunisation policy funding approaches differ by country and region. For those with or at risk of immunodeficiency, vaccination is variably funded from age 18 years or from age 50 years with a number of countries specifying that funding is limited to those who are severely immunosuppressed or identifying the categories of patients for whom vaccination is reimbursed (for example, stem cell transplant recipients, recurrent HZ). A number of these countries (for example, Switzerland) differentiate between those with or at risk of severe immunodeficiency (vaccination from age 18 years) and those with immunodeficiency (not categorised as severe) for whom vaccination is offered at a younger age than for their general population (age 50 versus age 65 years). Regarding patients with or at risk of severe immunodeficiency, differences were observed among countries in terms of the specific categories of patients identified as eligible for vaccination within their programme.

The majority of countries that fund vaccination programmes against HZ were also noted to fund childhood vaccination programmes against chickenpox (varicella). The UK do not have a national varicella vaccination programme, but do provide funding for vaccination of individuals in close contact with those considered particularly vulnerable to chickenpox and its associated complications.

3 Epidemiology and burden of disease

Key points

- Herpes zoster (HZ) is a disease that results from the reactivation of latent varicella zoster virus in the body's nervous system. Typically characterised by a painful, blistering rash, it is often associated with acute pain and itching. Among those with a history of varicella, the individual life-time risk of developing HZ is approximately 30%.
- Complications of HZ disease can be extensive and can contribute to morbidity and mortality. Both the risk of HZ and complications from HZ increase with age after 50 years and among individuals who are immunocompromised due to immunosuppressive conditions or therapies.
- Health Protection Surveillance Centre (HPSC) data from the sentinel GP surveillance programme for HZ were used to estimate rates of HZ episodes in primary care. Data from 2013 to 2022 indicate that rates of HZ episodes increased with age; mean rates were highest in those aged 75 to 79 years old (826 per 100,000 population).
- Hospital Inpatient Enquiry (HIPE) system data (which reflect the public acute hospital setting) were used to examine hospital discharges and mortality data for those admitted with a primary diagnosis of HZ. Data for the period 2013 to 2022 indicate:
    - A mean of 285 patient discharges and 2,626 bed days per annum, with almost 75% of discharges and 87% of bed days occurring in people aged over 50 years.
    - The mean number of discharges per year was highest for those aged 84 years and older (mean 40, range 26 to 53).
    - The longest average length of stay was in those aged 84 years and over (14.9 days).
    - There were 54 deaths in acute hospitals; 85% were in those aged 75 years and older, with almost half (46%) of all deaths occurring in those aged 84 years and older. These figures do not include individuals who may have died in the community as a result of HZ.
- International data shows that those who are immunocompromised have an increased incidence of HZ compared to the general population. Incidence rates

are highest in those undergoing haematopoietic stem cell transplant and solid organ transplant.

- Although mortality rates increase with increasing age, the overall HZ-mortality rate in Europe is generally low (0.039 per 100,000 population).
- The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to the persistence of chronic pain after the resolution of the acute rash. Other complications can include herpes zoster ophthalmicus, herpes zoster oticus, disseminated or recurrent HZ lesions, as well as neurological and cardiac complications.
    - PHN can significantly alter individuals' lives, inflicting debilitating pain, disrupting daily activities, sleep, and emotional wellbeing. In some it can lead to profound lifestyle changes, affect relationships, work, and overall quality of life.
    - There is substantial variability in the proportion of HZ cases that go on to develop PHN. International data indicate that the probability of PHN at 90 days increases with age. On the basis of a large Spanish study, the probability increases from 0.10 (a one in 10 chance) in 50- to 59-year-olds to 0.21 (one in five) in those aged over 80 years.
    - There is uncertainty over how long PHN symptoms persist; studies which measured those who had PHN at 90 days found that between 4% and 24.6% still experienced severe pain at nine months.
- HZ and associated complications such as PHN can contribute significant care and cost burden on both primary care and acute hospital services. Data from international studies suggest mean costs increase with age and are consistently higher for:
    - individuals who experience complications of HZ (such as PHN) compared with individuals with acute HZ
    - individuals with immunocompromising conditions compared with those without immunocompromising conditions.

3.1 Introduction

This chapter describes the epidemiology and burden of disease associated with herpes zoster. Herpes zoster (HZ), which is commonly known as shingles, is typically recognised by a painful blistering rash on the torso. HZ is caused by reactivation of

the varicella zoster virus (VZV). Primary infection with VZV results in varicella (chickenpox) which typically presents in children. After varicella infections resolve, the virus remains, and becomes latent in the body's nervous system. The virus may reactivate after a period of time, typically several decades later, resulting in HZ.

This chapter describes the incidence of HZ in Ireland and internationally, outlines the burden associated with this disease and its complications using both national and international data, and discusses available preventive and treatment options.

3.2 Natural history of HZ

As introduced in Chapter 2, HZ results from the reactivation of VZV from a latent infection state within the dorsal root ganglia of the body's nervous system. Primary infection, usually during childhood, results in varicella, during which latent infection is established.[3] During primary infection, VZV infects host cells of the adaptive immune system within lymphoid tissue of the immune system. The virus reconfigures these cells to reduce their immune functions and enhance their skin homing ability, so that these infected immune cells (T-cells) transport the virus to the skin and nerve ganglia.[93] In both primary infection and reactivated HZ disease, the virus counteracts local innate immune responses at the skin to allow it to spread and produce the characteristic vesicular rash.[93]

At both the skin and nerve ganglia, innate immune cells function to control the spread of VZV. Innate immune cells directly limit viral replication and also facilitate the adaptive immune response through the activation of T-cells. T-cells have been shown to be important against severity of varicella and HZ; early high T-cell responses are associated with milder varicella infection, whereas low VZV-specific T-cell responses are associated with more severe HZ and post-herpetic neuralgia (PHN).[93] In addition, antibodies are important in preventing primary VZV infection and controlling reactivation. VZV-specific antibody (specifically, immunoglobulin G or IgG) levels have a functional half-life of 50 years and help to limit the virus surviving and replicating by recruiting cells of the adaptive immune system to kill infected cells (antibody-dependent cell-mediated cytotoxicity) and by attaching to and blocking any virus particles they interact with (neutralising cell-free virus).[93]

HZ can occur at any age, although incidence of the disease has been shown to increase with age.[6, 94, 95] The increased incidence in HZ with age is associated with the age-related decline in VZV-specific cell-mediated immunity.[95] While the majority of cases occur in adults and cases in childhood are less frequent, childhood cases of HZ have been documented in children as young as four months.[14] Generally, HZ in children is less severe than in older individuals.[7] Apart from increasing age, additional factors associated with an increased risk of HZ include female sex,

ethnicity, family history, autoimmune diseases, comorbid conditions, physical injury and statin use.[2]

HZ disease is characterised by a vesicular skin rash, often associated with acute pain and itching. Areas of skin around the torso (termed, thoracic dermatomes) are most frequently affected. These dermatomes are supplied by nerve connections from spinal nerves, and correspond to specific spinal segments. Vesicle formation continues over a period of three to five days followed by progressive drying and crusting between day five and day seven. It can take between two to four weeks for the rash to resolve, after which time an individual may be left with permanent pigmentation changes and scarring around the affected areas where the rash occurred.[3, 4]

Prodromal symptoms include headache, myalgia, malaise, and photophobia, which typically last for two to three days.[4, 7] In immunocompetent individuals, the rash typically manifests in one or two thoracic dermatomes of the torso, and usually does not cross the midline as the virus is localised to specific ganglia.[7] It is possible for the rash to affect multiple dermatomes (termed disseminated zoster), which occurs more frequently in immunocompromised individuals and may appear similar in appearance to primary varicella disease.[4, 5] Additional atypical presentations of HZ have a greater risk of occurring in immunocompromised individuals and can include a prolonged and or complicated course of disease, recurrent HZ lesions, multiple dermatome involvement and lesions with chronic crusts or verrucous nodules.[7] Recurrence rates of HZ at eight years from an index HZ episode were estimated at 6.2% based on evidence from a US community population-based cohort study. There was a significantly higher rate of recurrence in those reported to be immunocompromised compared with those reported to be immunocompetent at the time of the index episode (HR: 2.35; 95% CI 1.35 to 4.08) and in those who experienced zoster-associated pain at 30 days or longer in the index episode (HR 2.80; 95% CI 1.84 to 4.27).[96]

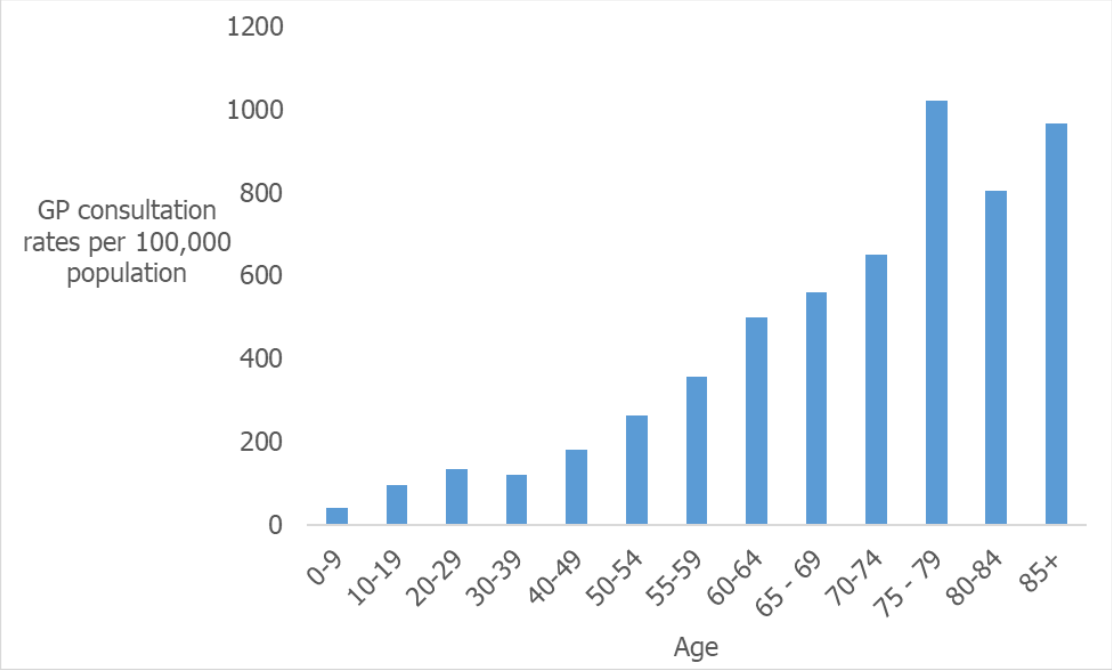
3.3 Incidence and prevalence of herpes zoster in Ireland

In Ireland, HZ is not categorised as a notifiable disease and only hospitalised cases of varicella are listed as notifiable.[97] As such, the presentation of HZ in the community in Ireland is estimated from data obtained from the sentinel surveillance programme for HZ, one of several sentinel general practice surveillance programmes for clinical diseases in Ireland.[98] The sentinel programme comprises a network of 90 general practices (representing 9 to 10% of the population) that report, on a weekly basis, the number of clinical episodes with HZ or varicella.[99]

The number of HZ episodes per 100,000 population in 2022 is presented by age group in Figure 3.1. The HSE advises that anyone who suspects they may have HZ

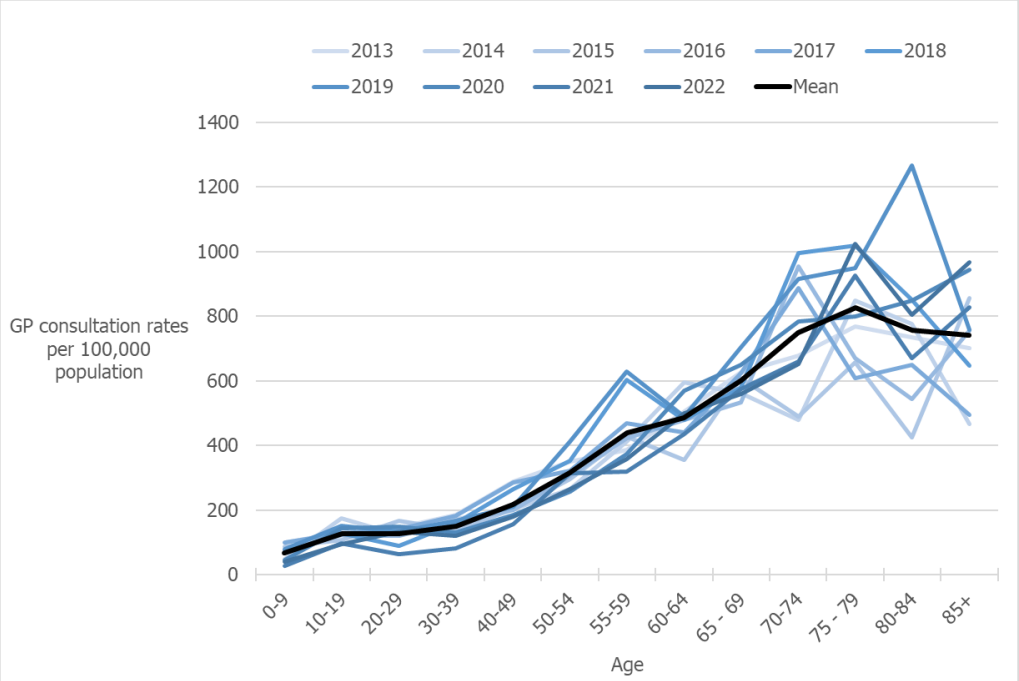
should see a GP as soon as possible, and so these data are expected to be reflective of the incidence of HZ cases that present clinically in the community.[100] Applying these rates to current population estimates, approximately 14,700 people get diagnosed with HZ by their GP each year. In 2022, HZ episode rates were highest in the 75- to 79-year age group with 1,022 episodes per 100,000 population, followed by those aged 85 years and older (966 episodes per 100,000).[99] Data for the past 10 years (2013 to 2022) are presented in Figure 3.2 and show a consistent association of increasing rate of episodes with increasing age. For the 10-year period 2013 to 2022, mean episode rates for HZ were highest in 75- to 79-year-olds (826 per 100,000 population). These data do not capture those who have HZ in the community, but do not present at the GP.

Figure 3.1 Episodes of HZ in primary care per 100,000 population (2022)



Source: GP sentinel data provided by HPSC[99]

Figure 3.2 Episodes of HZ in primary care per 100,000 population by age (2013 to 2022)



Source: GP sentinel data provided by HPSC[99]

3.4 Incidence and prevalence of herpes zoster internationally

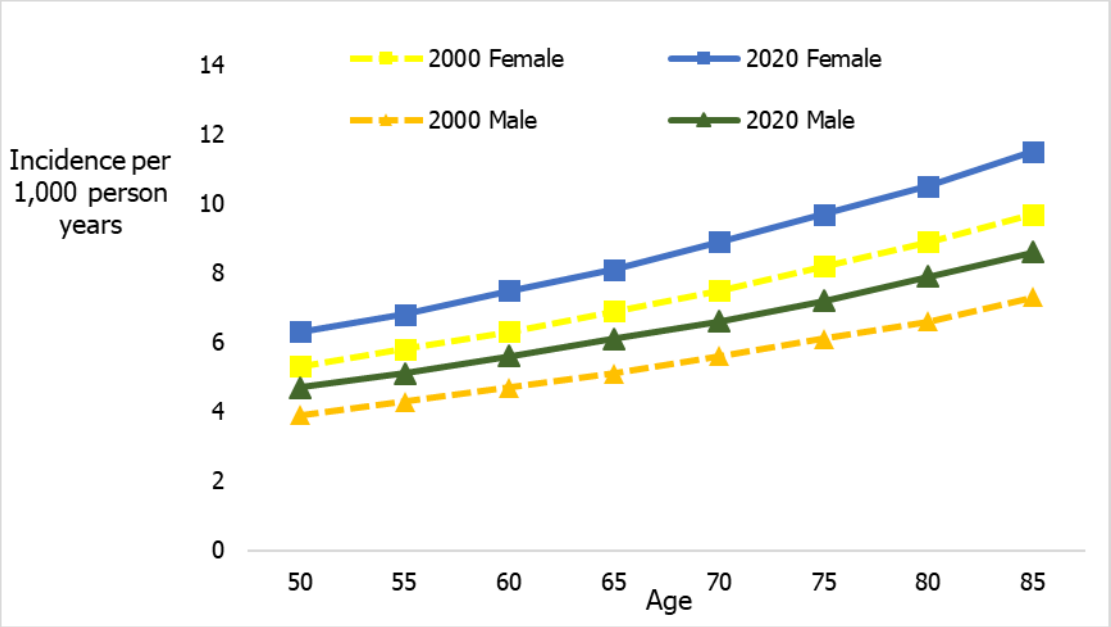
3.4.1 General adult population

A systematic review published in 2014 reported that the incidence rate of HZ in the general population ranged from 3 to 5 per 1,000 person years for North America, Europe and Asia-Pacific, based on 63 studies from 26 countries.[6] Similar results were reported in 2013 for the incidence rate of HZ in Europe, from 2.0 to 4.6 per 1,000 person years.[95] This study estimated an average HZ incidence for Europe of 3.4 ± 0.2 per 1,000 person years, based on nine studies.[95] Both studies reported that incidence of HZ increased with age after 50 years, while Pinchinat et al. noted that incidence rates were higher among women than men.[6, 95]

In addition, a meta-analysis of incidence of HZ worldwide among individuals aged 50 years and older, published in 2022, suggested that incidence increased with age, was higher in females compared to males, and increased with year of study data (Figure 3.3).[94] The difference in incidence between males and females was greater in younger age groups (e.g., 50 to 59 years) compared with older age groups (80+ years). The overall incidence rate in Europe, across age and sex, was estimated as 6.77 per 1,000 person years (95% CI: 6.14 to 7.48). This estimate aligns with those reported in the earlier systematic reviews, of 7 to 8 per 1,000 person years after 50

years of age for Europe (based on 9 studies),[95] and an estimated global incidence rate of 6 to 8 per 1,000 person years at 60 years of age.[6]

Figure 3.3 Estimated incidence of HZ in Europe 2000 and 2020 by age and sex



Source: Curran et al.[94]

Two reviews reported an increase in the incidence of HZ over time.[6, 94] Kawai et al. identified studies from six countries that reported an overall increase in the incidence of HZ over time, typically between the 1990s and 2000 to 2010.[6] According to pooled analyses of year classes by Curran et al., worldwide incidence of HZ among adults aged 50 years and over increased from 6.6 per 1,000 persons before 1998 to 7.4 per 1,000 persons from 2013 to 2022.[94] Incidence of HZ varies by continent and the finding of increased incidence may be influenced by changes in the geographic distribution of studies over time.

The lifetime risk (assuming a life expectancy of 78 years) of VZV reactivation, that is of experiencing HZ, has previously been reported as approximately 30%.[1] Analysis of data from the 2015 Health Survey for England, an annual cross-sectional representative survey of households in England, explored risk factors associated with HZ.[101] Consistent with the studies cited previously, after adjusting for a range of factors, increasing age and female sex were associated with increased odds of HZ. Other potential risk factors (white ethnicity, moderate physical activity seven days per week, and digestive disorders) were identified, with the study authors suggesting future studies explore these associations to investigate possible mechanisms.[101]

3.4.2 Immunocompromised adults

The incidence of HZ is higher in those individuals who are severely immunocompromised due to immunosuppressive conditions or therapies.[102] Disease can also be more severe in these populations.[102] There are numerous conditions that can affect immunity and increase an individual's chances of developing HZ, and, as a consequence, there is substantial variation in the elevated risk of HZ across conditions.

A systematic review published in 2019 reported the incidence of HZ among specific subpopulations in Spain, including people living with diabetes, COPD, HIV, cancer, solid organ transplant recipients, and adults with immunosuppression due to rheumatic diseases.[103] The incidence was similar in those with diabetes, COPD, cardiovascular, and rheumatic diseases (means between 9.4 and 11.0 per 1,000 person-years). Incidence was lowest in those with asthma (mean 6.9 per 1,000 person-years). The reported incidence for the general population ranged from 2.1 to 5.5 per 1,000 person-years.

Before the introduction of combined antiretroviral therapy (cART), incidence of HZ was substantially increased in adults with HIV.[104] Numerous recent studies have shown decreases in incidence of HZ in individuals with HIV, and this is associated with increased treatment using cART. The reported pooled incidence across 11 studies was 23.0 per 1,000 person-years.[104] However, there was a strong time trend with incidence decreasing in more recent studies. It should also be noted that mean age of study participants ranged from mid-thirties to early-forties, when HZ incidence in the general population is typically low.

Individuals that have undergone haematopoietic stem cell transplant (HSCT) are at substantially increased risk of HZ. A systematic review of studies in US HSCT populations reported incidence between 42.4 and 94.3 per 1,000 person-years.[105] The mean age of study participants was 55 in four of the five included studies.[105] A Swedish study reported an incidence of 103 per 1,000 person-years with a mean 2.4 years of follow-up.[106] Infections predominantly occurred in the first year after transplant, suggesting that the elevated risk may not persist over the longer term. The use of at least one year of post-transplant antiviral prophylaxis was associated with lower HZ cumulative incidence.[105]

Recipients of solid organ transplants have also been identified as a cohort at elevated risk of HZ. A 2021 systematic review identified 12 studies reporting incidence in this population.[107] The incidence varies with transplant type, ranging from 14.2 per 1,000 person-years for kidney transplant recipients to 41.2 per 1,000 person-years for lung transplants. The pooled incidence across solid organ transplants was 17.2 per 1,000 person-years.

As distinct subpopulations with increased risk of HZ tend to have different demographic profiles to the general population, it is challenging to determine the incidence of HZ in an equivalent general population. For this reason, with few exceptions, studies have not reported the relative risk of HZ compared to a general population for the included subgroups. It is also important to note that the follow-up in the included studies was usually one to two years on average, so there is limited evidence on whether the elevated risk changes over the longer term.

3.5 Burden of disease

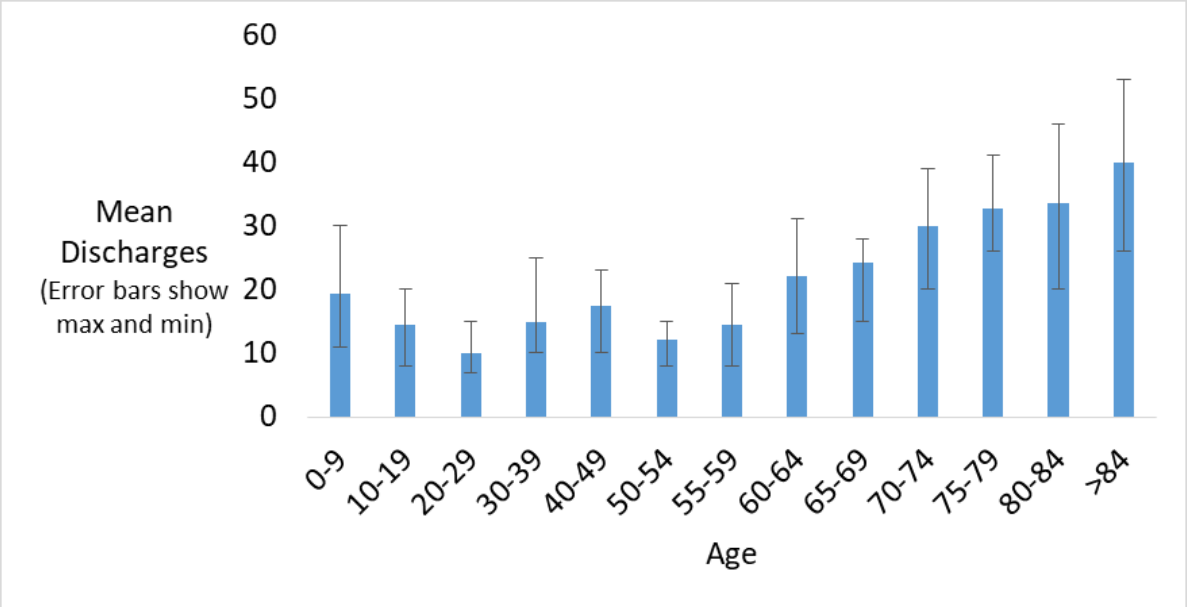
3.5.1 General practitioner attendance

Irish data indicate that typically a GP will see one to three cases of HZ per month.[108] HZ mostly presents in patients age 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.[108] As outlined in section 3.3, a trend of increasing episode rate with increasing age has been observed, with those aged 70 and over most likely to visit the GP.

3.5.2 Hospitalisations

Data from the Hospital Inpatient Enquiry System (HIPE) in Ireland were used to examine hospital discharges with a primary and secondary diagnosis of HZ.[109] The average annual number of inpatient discharges by age group for the past 10 years (2013 to 2022) is provided in Figure 3.4. The mean annual number of patient discharges with a primary diagnosis of HZ was 285, with almost 75% of cases occurring in people aged over 50 years. The mean number of discharges per year was highest for those aged 84 years and older (mean 40, range 26 to 53) and lowest for those aged 20 to 29 years (mean 10, range 7 to 15). The mean annual number of day cases was low for all age groups with the highest mean number of cases in the 80 to 84 years age group (mean 5, range 0 to 9).

Figure 3.4 Mean annual inpatient discharges with a primary diagnosis of HZ from acute hospitals in Ireland, by age group (2013-2022)

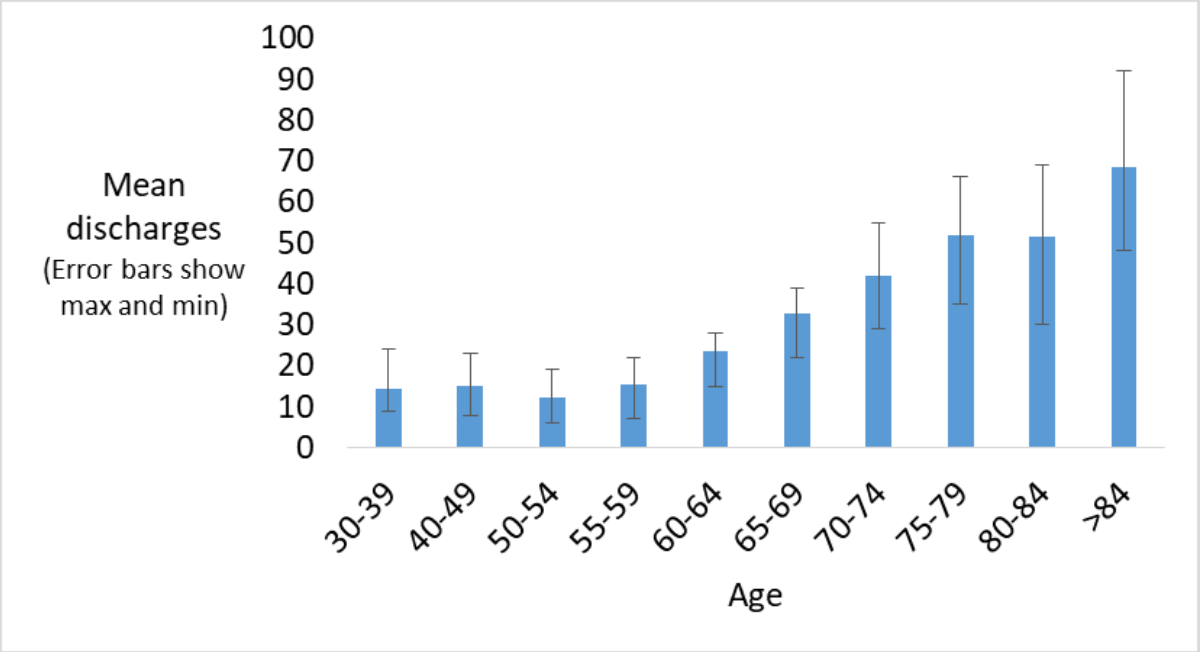


Source: Hospital Inpatient Enquiry System[109]

Note: Discharges for day cases are not included in this graph as much of the data were censored due to low number of events.

HIPE data were also reviewed to assess the number of people discharged with a secondary diagnosis of HZ (Figure 3.5). The mean annual number of discharges per age group ranged from 12 per year in those aged 50 to 54 years to a mean of 69 per year in those aged 84 years and over.

Figure 3.5 Mean annual inpatient discharges with a secondary diagnosis of HZ from acute hospitals in Ireland by age group (2013 to 2022)

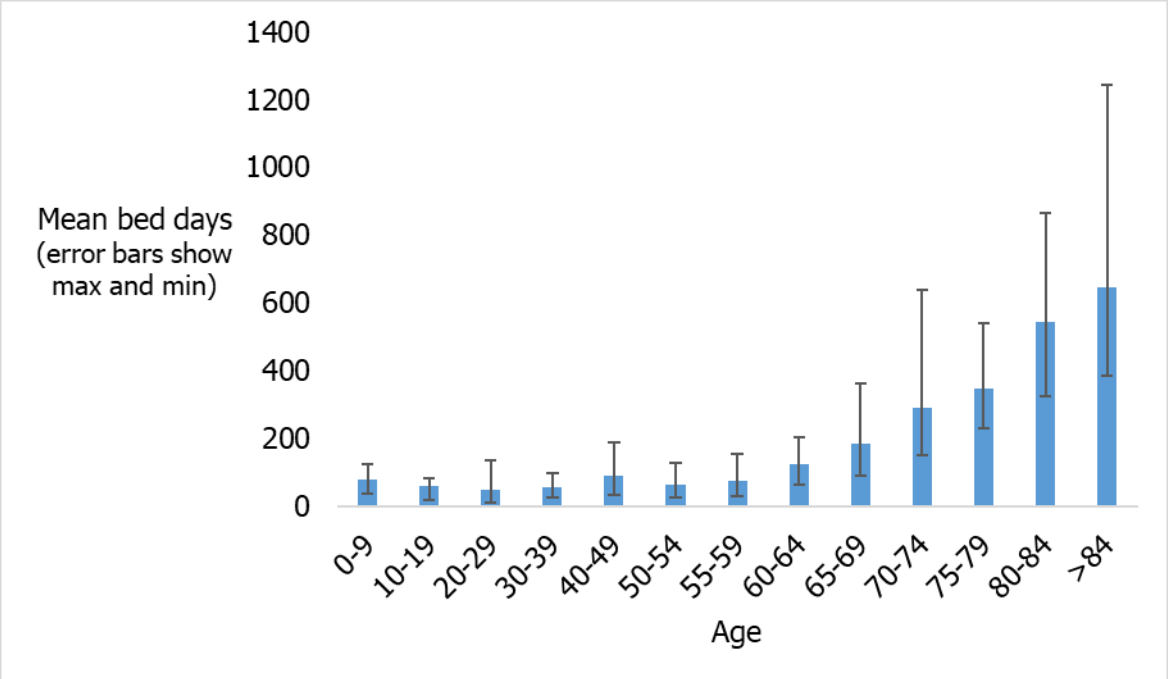


Source: Hospital Inpatient Enquiry System[109]

Notes: Graph only includes data for age bands from 30 years and over as for all younger age bands there were 5 people or fewer in each group, so the data were censored.

The mean annual number of bed days was 2,626 (range 2,084 to 3,303), with 87% (range 83% to 90%) of these occurring in people aged 50 years and older. The longest average length of stay for those with a primary diagnosis of HZ was observed in those aged 84 years and over (14.9 days) and the shortest average length of stay was for those aged zero to nine years (3.8 days). For individuals aged 50 years and over, the average length of stay for those with a primary diagnosis of HZ increased with increasing age. The mean annual number of bed days by age group from 2013 to 2022 is reported in Figure 3.6.

Figure 3.6 Mean annual number of bed days for those with a primary diagnosis of HZ by age group (2013 to 2022)



Source: Hospital Inpatient Enquiry System[109]

A 2014 systematic review of the incidence and complications of HZ reported that hospitalisation rates increase with age, and that the majority of hospitalisations occur in adults aged 50 years and older.[6] Three studies reported HZ-associated hospitalisation rates for adults aged between 60 and 69 years; estimates ranged from 10 per 100,000 (USA, 1992 to 2004) to 13 per 100,000 (Australia, 1998 to 2005) and 31 per 100,000 (Germany, 2007 to 2008). Higher rates of HZ-associated hospitalisation were reported for adults aged 80 years and older, ranging from 15.7 per 100,000 (Spain), to 96 and 300 per 100,000 (Australia).[6]

In England, based on Hospital Episode Statistics from 2004 to 2013, there were on average 4,546 admissions per year due to HZ. The average annual admission rate due to HZ was 8.8 (95% CI: 8.6 to 9.0) per 100,000 population.[110] The general population (excluding immunocompromised individuals) accounted for 82% of the admissions with the majority of HZ-associated hospital admissions (71%) occurring among those aged 60 years and over. In addition, female patients accounted for 57.9% of HZ admissions.[110] The average length of stay for HZ admissions was 9.2 (95% CI: 8.6 to 9.8) days, with an average cost per admission of £2,872 (based on 2013/2014 tariffs).[110]

In Spain, according to the Spanish minimum basic data set for 2016 to 2019, the hospitalisation rate for admissions diagnosed with HZ was 17.74 per 100,000 population, with 90.3% of patients admitted aged greater than 50 years and 45.8%

of patients admitted aged 80 years and older.[111] The hospitalisation rate during the same period increased with age reaching 110.96 per 100,000 persons (95% CI: 109.0 to 112.9) in patients aged 80 years and older. The median length of stay was seven days (interquartile range: 4 to 13 days) and it did not differ by age or sex. Limitations of this data set include that multiple hospitalisations could occur for the same patients, and it included any diagnosis of HZ, so that HZ may not have been the primary cause of hospitalisation.[111] A larger number of hospitalisations occurred from complicated cases of HZ (10.62 per 100,000 population) than from cases that did not include complications (7.12 per 100,000 population). Hospitalisations in patients considered at increased risk of HZ due to underlying conditions or immune suppression are presented in Table 3.1. There were 3,078 hospitalised cases (11.1% of total HZ hospitalisations) in patients with solid tumours, and 1,237 hospitalised cases (4.5% of total HZ hospitalisations) among patients with haematological malignancies. The percentage of patients presenting with complications ranged from 47.2% (HIV) to 58.3% (Rheumatoid arthritis).[111]

Table 3.1 Hospitalisations due to HZ among patients at increased risk of HZ in Spain between 2016 and 2019

Patient group	Uncomplicated cases N (%)*	Complicated cases N (%)	Total cases N
Solid tumours	1,501 (48.8)	1,577 (51.2)	3,078
Haematological malignancies	543 (43.9)	694 (56.1)	1,237
RA	253 (41.5)	356 (58.3)	609
HIV	292 (52.8)	261 (47.2)	553
SOT	231 (44.1)	293 (55.9)	524
HSCT	123 (5.9)	145 (54.1)	268

Key: HIV – human immunodeficiency virus; HSCT – haematopoietic stem cell transplant; RA – rheumatoid arthritis; SOT – solid organ transplant; *N – number of cases; % - percentage of cases
Source: Corcuera-Munguia, 2023[111]

3.5.3 Complications

European consensus-based (S2k) guidelines on the management of HZ note that patients at risk of complicated and severe courses of HZ can be identified by the presence of a series of risk factors, including age older than 50 years, prodromal or acute pain, and immunosuppression (including cancer, haemoglobinopathies, HIV infection, solid organ and bone marrow transplant recipients), and patients receiving immunosuppressive therapies.[3] Complications of HZ disease can be extensive and can contribute considerably to morbidity and mortality risk. The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to the persistence of chronic pain after the resolution of the acute cutaneous HZ lesions. Other complications can include herpes zoster ophthalmicus (HZO), herpes zoster oticus,

recurrent or disseminated HZ lesions, as well as neurological and cardiac complications.[3]

3.5.3.1 Post-herpetic neuralgia

PHN can significantly impact on individuals' lives, causing debilitating pain that can persist long after the shingles rash subsides. For some, PHN becomes a chronic condition disrupting daily activities, sleep, and emotional well-being. It can lead to profound lifestyle changes, affecting relationships, work, and overall quality of life. PHN causes a loss of physical function, manifesting as fatigue, loss of appetite, weight loss, reduced mobility, decreased activity levels, sleep disturbances (particularly insomnia), and reductions in overall health.[112, 113] Basic tasks like bathing, dressing, and eating, as well as more complex activities such as travel, household chores, and shopping, can become challenging.[112] Older patients with PHN may face institutionalisation and a loss of autonomy.[114] Additionally, reduced independence and decreased participation in social events can lead to social withdrawal, isolation, and a loss of social connections among PHN patients.[112, 114] PHN can also impact the psychological well-being of patients.[113, 115]While psychosocial scores tend to improve for patients who fully recover from the acute symptoms of HZ, they often remain low for those who develop PHN.[115] Individuals experiencing intense pain are at a heightened risk of anxiety and depression compared to those with milder pain.[112, 113] Difficulties maintaining concentration are commonly reported among patients with PHN.[114] Management of PHN is complex and may involve multimodal therapy including a combination of oral and topical pain relief, regional nerve blocks, antidepressants, anticonvulsants and or physical therapy. Complete resolution of symptoms is rare and management is complicated by the age profile of the patient population, many of whom may be frail with multiple comorbid conditions.[116]

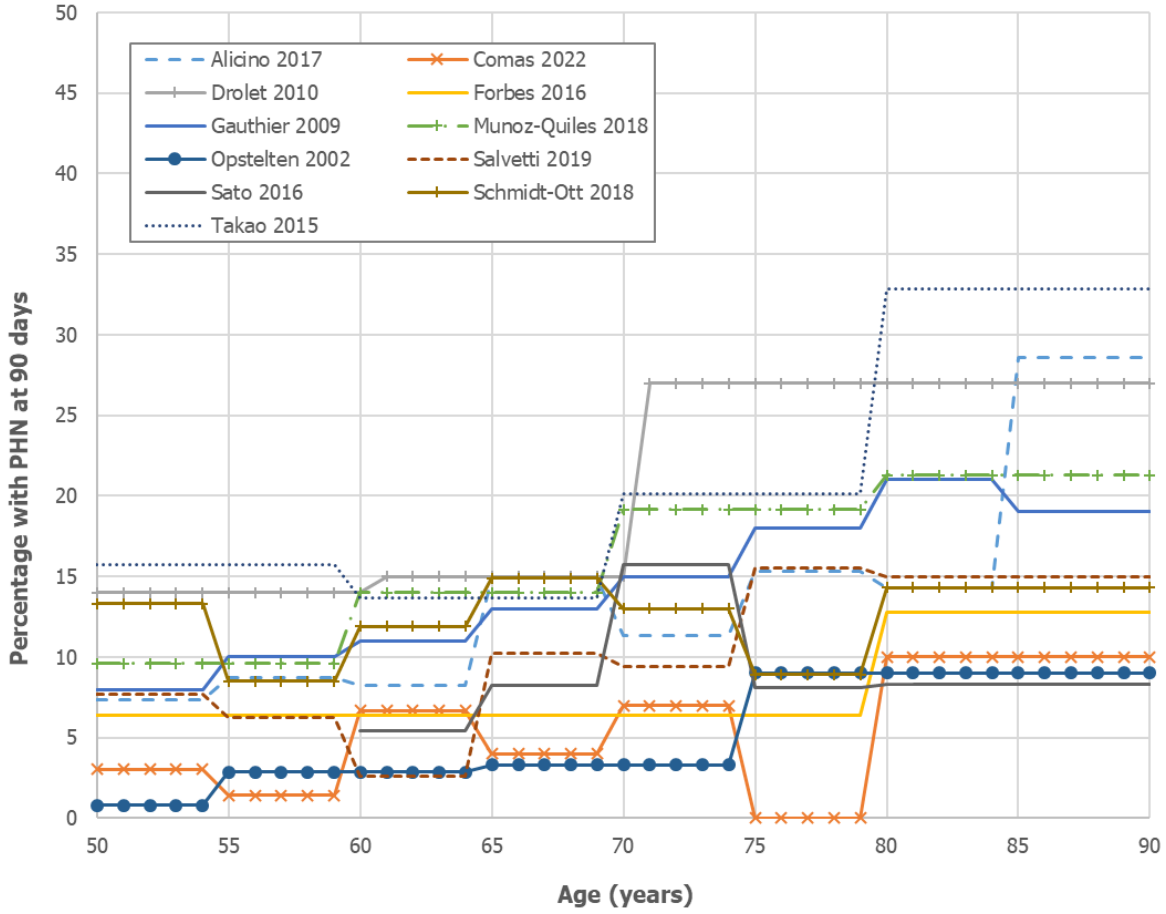
PHN is the most frequent complication of HZ disease, with estimates reported by one systematic review in individuals with HZ disease ranging from 5% to more than 30%.[6] Differences in the case definition of PHN have been noted which may contribute to the wider range in estimates; other contributing factors may include varying prevalence of other risk factors, population demographics and differing study designs.[6] The authors of a 2016 systematic review of risk factors for PHN noted that there is no consensus regarding the exact definition of PHN; definitions of PHN from 19 studies ranged from presence of pain at one month to at six months after rash onset.[117] Definitions may describe PHN as a persistent pain that lasts at least 30 days after the acute infection or after all lesions have crusted,[4] or pain lasting for more than 90 days after rash onset.[3] Public Health England have previously defined PHN as nerve pain persisting for three months or longer following the resolution of the acute skin lesions.[118]

Considering the pathophysiology of HZ and definitions suggested from trials on antiviral treatment and HZ vaccination, a preference has been expressed in the literature for defining PHN as the presence of clinically meaningful pain persisting for more than 90 days from rash onset.[6]

PHN is more likely to occur in older adults, who are also more likely to have longer lasting and more severe pain. A 2014 systematic review reported age-specific risk of PHN in patients with HZ for 15 studies from 12 countries.[6] The risk of PHN ranged from 3.4% to 19.3% for patients aged 50 to 59 years, 4.9% to 28.7% for patients aged 60 to 69 years, 7.9% to 37.3% for patients aged 70 to 79 years, and 7.8% to 40.5% for patients aged 80 years and older.[6] A 2016 systematic review of risk factors for PHN also reported that older age was significantly associated with an increased risk of PHN.[117] The mean age of study participants ranged from 52.3 to 67.7 years and the increased odds of PHN per 10 year increase in age ranged from 1.34 (95% CI 1.10 to 1.63) to 3.11 (95% CI 1.79 to 5.23) based on eight studies.[117]

Using data from 11 studies[119-129] reporting PHN at 90 days by age group, it is apparent that there is substantial variability in the proportion of HZ cases that go on to have PHN (Figure 3.7). The largest of the included studies, by Munoz-Quiles et al., was conducted in Spain and included data on 87,086 cases of HZ.[124] It can be seen that the probability of PHN at 90 days increases with age. On the basis of the Munoz-Quiles study, the probability increases from 0.10 (a one in 10 chance) in 50- to 59-year-olds, to 0.14 in 60- to 69-year-olds, 0.19 in 70- to 79-year-olds, and finally to 0.21 in those aged over 80 years.

Figure 3.7 Percentage of cases of herpes zoster that go on to have post-herpetic neuralgia at 90 days after initial infection



A systematic review, published in 2014, reported that the duration of PHN was highly varied, with evidence from included prospective cohort studies suggesting that 30% to 50% of patients with PHN experience pain lasting for more than one year.[6] In more recent studies from Spain, Italy, Germany and Japan, while there was variability among studies including in the definition of PHN, lower proportions of individuals with PHN were reported to have continued pain at one year. In a Spanish study (HZ cases=598) among patients with at least one year of follow-up, 18.4% of those with PHN at 90 days continued to report PHN one year after the onset of HZ.[119] In another Spanish study (HZ cases= 459), of the patients with PHN, 20% patients had PHN persisting until day 180; while 4% had PHN persisting 270 days after rash onset.[120] In an Italian study (HZ cases=721), 15.0% of those with PHN reported persistent PHN at day 180 with 7.5% still reporting PHN at day 270.[126] In a German study (HZ cases =513), of those with PHN at 90 days, 41.0% reported PHN at six months and 24.6% at nine months.[128] In a Japanese study (HZ cases=615) of those with PHN, 39.5% to 44.3% reported moderate to severe pain

at six months while 10.5% reported moderate to severe pain nine months after rash onset.[127, 129] Depending on the age at which a person develops HZ, as many as 5% to 10% of cases may experience symptoms of PHN lasting a year or more.

Several clinical features of acute zoster were reported as risk factors for PHN in a 2016 review. Summary rate ratios (RR) indicated that the presence of a prodromal period (RR 2.29, 95% CI: 1.42 to 3.69; n=5 studies), severe acute pain during the acute zoster period (RR 2.23, 95% CI: 1.71 to 2.92; n=8 studies), rash severity (RR 2.63, 95% I: 1.89 to 3.66) and ophthalmic involvement (RR 2.51, 95% CI: 1.29 to 4.86; n=3 studies) were associated with increased risk of PHN.[117] Similarly, a 2021 systematic review of independent risk factors for PHN reported acute severe pain, prodromal symptoms and severe rash as risk factors for PHN.[130]

A 2020 systematic review reported on the risk of PHN in immunocompromised adults with HZ in the US.[105] The risk of developing PHN ranged from 6% to 45%, depending on the immunocompromising condition: ranging between 6% and 41% for those with a history of HSCT (n=6 studies); between 7% and 45% for those with a history of solid organ transplant (n=3 studies); between 6% and 40% for those with haematological malignancies (n=3 studies); 9% for those with solid tumour malignancies (n=1 study); and 6% in those with HIV (n=1 study).[105]

3.5.3.2 Herpes zoster ophthalmicus

Herpes zoster ophthalmicus (HZO) is a complicated disease course that affects the ophthalmic nerve (V1), a sensory nerve responsible for providing sensory nerve supply (termed innervation) to the scalp, eyes, nose and forehead.[131] HZO commonly results in swelling and vesicular rash of the forehead, scalp and eyelids.[132] HZO can result in serious complications that include inflammation of the eye and surrounding tissues, muscular weakening, secondary infections (acute or delayed keratitis, uveitis, conjunctivitis, scleritis, eyelid retraction, oculomotor palsies, paralytic ptosis, secondary bacterial cellulitis, secondary glaucoma, optic neuritis or acute retinal necrosis with the risk of bilateral blindness).[3] In addition, patients at increased risk due to age or immunocompromised status may experience persistent or recurrent pain in the affected region after experiencing HZO.[132]

According to a 2014 systematic review, the reported risk of HZO ranged from 10.1% to 14.9% among patients in the general population in four countries (USA, France, the Netherlands and Saudi Arabia).[6] There was a wide range in the reported risk of eye complications, from 30% to 78% from four studies and as low as 2.5% in a population-based study in the USA.[6] A 2020 systematic review investigating the risk of HZ in immunocompromised adults in the USA noted that four studies reported estimates for HZO of ≤1% among adults following HSCT (n=3 studies) or solid organ transplant (n=1 study).[105] A 2017 systematic review reported on the

association between development of HZO and subsequent risk of cardiac and cerebrovascular events.[133] Considering the association between HZO and acute cardiac events, the authors reported the relative frequency of myocardial infarction to be significantly higher in the first week after disease onset based on the findings of one study. Meta-analysis of data from self-controlled case series studies indicated that the association between HZO and cerebrovascular events persisted over time with pooled odds ratios of 1.85 (95%CI: 1.09 to 3.12) and 4.42 (95% CI: 2.75 to 7.11) relative to baseline risk within the first three months and the first year of HZO onset, respectively.[133] In addition, a 2017 systematic review found that the relative risk of stroke was higher during the first month following HZO (relative risk 2.05; 95% CI: 1.82 to 2.31), with this risk remaining high at 12 months follow-up.[134]

3.5.3.3 Recurrent zoster and other complications

A 2023 longitudinal follow-up study of the pharmacologic treatment used for patients with HZ in Colombia reported the number of recurrent cases of HZ, defined as any episode of HZ that occurred at least 90 days after the initial episode.[135] From a total of 2,978 patients with any diagnosis of HZ, the most frequent diagnosis was HZ without complications, which accounted for 55.9% (n=1,665) of cases. The remaining diagnoses included central nervous system HZ (n=1,192; 40%), HZ with other complications (n=74; 2.5%) and ocular HZ (n=27; 0.9%). A total of 2.3% (n=69) of cases experienced recurrent HZ. Disseminated zoster occurred in 0.7% (n=20) of cases.[135]

In a 2014 systematic review investigating global HZ incidence, nine studies examined recurrent cases of HZ. Studies with long-term follow-up periods tended to report higher risks of recurrent HZ.[6] However, the authors noted that risk of recurrence may vary between studies by inclusion of individuals at increased risk of HZ and HZ-related complications, such as inclusion of those with an immunocompromised immune status. Studies with one to two years follow-up reported a risk of recurrent HZ of less than 1.5%. In comparison, three studies with 8-, 16-, and 20-year follow-up periods reported 6.2%, 4.7%, and 5.3% of patients experiencing recurrent HZ.[6]

A 2017 systematic review reported on the risk of stroke following an acute episode of HZ. Data from nine studies indicated an elevated risk of stroke with HZ, which was highest in the first month following the acute HZ episode and persisted for at least one year.[134] The relative risk of stroke was 1.78 (95% CI: 1.70 to 1.88) in the first month, 1.43 (95% CI: 1.38 to 1.47) over the first three months and 1.20 (95% CI: 1.14 to 1.26) in the first year after the HZ episode.[134]

3.5.4 Quality of life

People with HZ have a diminished quality of life. A systematic review and meta-analysis compared quality of life in those with HZ to quality of life in a matched population.[136] Overall physical quality of life (as measured by the physical component score of short-form 12) was estimated to be around 15% lower in individuals diagnosed with HZ when compared to normative data; this difference was statistically significant. Overall mental wellbeing, as measured on the same questionnaire was about 13% lower in those with HZ.[136]

The burden of PHN on health-related quality of life may be presented as quality-adjusted life years (QALYs) lost or gained. QALYs are estimated using self-reported utilities (on a scale of one (perfect health) to zero (death)), or health-related quality of life measures. Data from international studies in individuals with PHN report a wide range of utility values; however, in general, they indicate that the impact on health-related quality of life increases with age with older individuals experiencing greater burden. Mean health-state utility values for individuals aged 50 and over with PHN measured at day 90 range from 0.643[137] to 0.825[138]. In 50- to 59-year-olds, mean health-state utility values at day 90 are between 0.701[137] and 0.730[139], while they range between 0.614[137] and 0.654[140] in those aged 80 years and over. Applying absolute utility values to Irish age-specific baseline utility values (Table 6.2[141]) suggests that the decrement in utility more than doubles for those aged 85 years and over relative to that for those aged 50 to 55 years old.

3.6 Mortality

Irish mortality data for HZ from the HIPE system are presented in Table 3.2.[109] For the 10-year period between 2013 and 2022, there were 54 deaths in acute hospitals where the person had a primary diagnosis of HZ. Eighty-five percent (n=46/54) of deaths were in those aged 75 years and older with 46% (n=25/54) occurring in those aged 84 years and older. These data do not account for anyone who may have died in the community as a result of HZ.

Table 3.2 Total number of deaths with a principal diagnosis of HZ in acute Irish hospitals from 2013 to 2022, by age group.

Age Group	Number of deaths*
0-9 years	0
10-19 years	0
20-29 years	≤5
30-39 years	0
40-49 years	≤5
50-54 years	0
55-59 years	0
60-64 years	0
65-69 years	≤5
70-74 years	≤5
75-79 years	11
80-84 years	10
>84 Years	25
Total	54

Source: Hospital Inpatient Enquiry System[109]
Note: *Where events are ≤5 these data are suppressed and therefore the true value is somewhere between 1 and 5.

A 2014 systematic review of the global incidence and complications associated with HZ reported that HZ mortality ranged from 0.017 to 0.465 deaths per 100,000 person-years from 10 studies, with the majority of deaths in adults aged 60 years and over.[6] A 2015 systematic review investigating HZ-related mortality in Europe found that overall, the mortality rate from HZ was generally low, with an overall trend of higher mortality incidence rate in older age groups, occurring from the age of 70 to 74 years.[142] The same study reported that the median WHO estimate for overall HZ mortality incidence for 2011 was 0.039 per 100,000 population, but that case fatality rates (CFR) and hospital fatality rates (HFR) varied between countries. In the UK, CFRs increased from 1 per 100,000 in those aged 45 to 65 years, to 61 per 100,000 in those aged 65 years and older.[142] The reported HFRs varied from 0.4% among patients aged 60 to 69 years in Portugal, to 7.1% among those aged greater than 80 years in Spain. The HFRs of other countries were typically below 1% in those aged less than 75 years.[142]

According to the Spanish Minimum Basic Data Set (MBDS) for 2016 to 2019, the mortality rate associated with HZ hospitalisations was 1.2 deaths per 100,000 persons (95% CI 1.15 to 1.25) and the CFR was 6.75% (95% CI 6.45 to 7.05).[111] The mortality rate increased with increasing age, with the lowest rates observed in patients aged under 50 years (0.04 deaths per 100,000 persons (95% CI 0.03 to 0.05)) and the highest at 10.65 deaths per 100,000 persons (95% CI 10.05 to

11.25) in patients aged 80 years and older. The mean incidence of deaths due to HZ per year (2004 to 2013) identified in English Hospital Episode Statistics was 0.31 per 100,000 person-years (95% CI 0.28 to 0.34), with the highest incidence of deaths per year occurring in those aged 60 years and over (mean=1.38, 95% CI 1.23 to 1.50).[110] However, the authors noted that comparison with the Office of National Statistics mortality data indicated a high level of uncertainty in this estimate.

3.7 Transmission rate of HZ to cause varicella

Someone with HZ can transmit VZV to someone who has not had varicella and is not immune, but someone with varicella cannot cause HZ in another person. Virus transmission is through direct contact with the fluid from shingles rash blisters or breathing in virus particles that come from the blisters.[143] There are limited data available on the rate of these transmissions. The household transmission rate of HZ (to cause varicella) is estimated at 15.5%, however this estimate is based on 70-year-old data and refers to the proportion of family contacts under 15 years of age without previous history of varicella who developed varicella after close contact with a family member with HZ.[144] The estimated transmission rate among family contacts decreased to 8.1% when including all ages without previous history of varicella.[144] Additional estimates of transmission can be derived from a study of surveillance data from school and day-care settings collected over eight years in Philadelphia (2003-2010). At least one other person was secondarily infected with VZV in 9% of 290 HZ cases, although this was considered to be an underestimate.[145] It was noted that HZ cases were as likely as varicella cases to be associated with clusters of more than two secondary cases, and that the severity of secondary varicella did not differ after exposure to HZ or varicella. Moreover, lesion size and location were not associated with identification of secondary cases in this study. The study noted that with increasing varicella vaccine coverage, transmission from individuals with HZ will likely play a proportionally greater role in VZV transmission.[145]

This section refers to natural transmission of VZV to close contacts by individuals who have developed HZ. This is distinct from the potential risk of transmission of vaccine-strain VZV that has been suggested as a theoretical risk, but laboratory evidence of this occurring has not been documented.[20, 146]

3.8 Treatment for HZ

The main aim of treating HZ cases is to reduce the duration of skin lesions, manage pain and minimise the risk of complications.[147] In the absence of risk factors associated with increased likelihood of developing complications, in the general population aged under 50 years, HZ is typically a self-limited disease that does not require antiviral treatment.[148] As summarised in Table 3.3, the HSE recommends

prescribing an oral antiviral within 72 hours of onset of rash in all patients over 50 years of age who develop HZ, in order to reduce the risk of PHN.[92] In addition, the prescribing of oral antivirals is recommended within 72 hours of onset of rash for patients with:

- herpes zoster ophthalmicus
- Ramsey Hunt syndrome
- severe atopic dermatitis/eczema
- rash affecting arms, legs, neck or genital areas
- moderate or severe pain
- moderate or severe rash
- immunocompromised patients (for whom referral to secondary care should be considered).

The window for prescribing antivirals can be extended to up to one week after onset of rash for patients for whom any of the following conditions are met:

- high risk of severe shingles or continued vesicle formation
- older age
- immunocompromised
- severe pain
- multidermatomal rash.

In addition, the HSE recommends seeking secondary care advice in patients who are:

- pregnant or breastfeeding
- immunocompromised
- forming new vesicles after seven days of antiviral treatment
- experiencing recurrent HZ
- experiencing ophthalmic HZ with Hutchinson's sign, visual symptoms or an unexplained red eye.

European consensus-based guidelines for the management of HZ, published in 2016, recommend early treatment of acute HZ associated pain using systemic analgesics in accordance with the WHO pain ladder.[147] Given the neuropathic component, for those with moderate to severe pain or where other risk factors for PHN are present, the guidelines recommend that supplementing with a tricyclic antidepressant (for example, amitriptyline) or antiepileptic (for example, gabapentin or pregabalin) drug should be considered.[147] These guidelines suggest against the application of local anaesthetic agents for the treatment of acute HZ-associated pain.[147] A 2014 Cochrane review of the efficacy of topical lidocaine for chronic neuropathic pain in adults found no evidence from good quality randomised controlled studies in support

of its use. However, limited evidence from individual studies, mostly in patients with PHN, indicated that it may be effective in treating neuropathic pain in some patients and is well tolerated in the short term.[149]

Lidocaine 700mg medicated plaster (Versatis®) is licensed in Ireland and has been reimbursed under the Community Drug Schemes (CDS) in Ireland since 2010 for the relief of neuropathic pain associated with HZ.[150] In 2017, the HSE Medicine Management Programme (MMP) reviewed and amended the process for application for reimbursement for this treatment, requiring all patients to be approved by the MMP prior to the initiation of treatment with Lidocaine 700mg medicated plaster (Versatis®). A further review was conducted in 2021 to update clinical evidence relevant to the use of this medicinal product. Detailed guidance can be found in the MMP Prescribing and Cost Guidance publication.[151]

Table 3.3 HSE guidelines for the treatment of HZ

Drug	Dose	Duration
1st line option		
Valaciclovir	1g every 8 hours.[a]	7 days If immunocompromised, continue for 2 days after crusting of lesions.
2nd line option		
Aciclovir	800mg five times daily. Doses to be taken five times a day at approx. 4 hourly intervals, during waking hours.[a]	7 days If immunocompromised, continue for 2 days after crusting of lesions.
3rd line option		
Famciclovir	500mg every 8 hours.[a]	7 days If immunocompromised, 10 days and continue for 2 days after crusting of lesions.

Key:[a] – Dose reduction in patients with renal impairment
Source: HSE Shingles (Herpes Zoster) Antiviral Prescribing[92]

3.9 Economic burden of HZ

Herpes zoster and its complications represent a significant burden for patients, resulting in considerable morbidity. In addition to the direct health-related burden experienced by patients, HZ and its complications, such as PHN, can contribute significant care and cost burden on primary-care resources. Direct costs associated with HZ, such as healthcare costs and resource utilisation, tend to be higher for older patients, whereas indirect costs, such as work time lost, are higher for younger patients.[152] The impact of HZ and PHN on the productivity of employed individuals was assessed in a prospective study of general population individuals aged 50 years

(n=88), with follow-up of six months.[153] Absenteeism relating to HZ was mostly reported in the acute phase of HZ, with 87% of employed participants reporting productivity losses as a result of absenteeism and/or presenteeism, for a mean of 72 hours lost per subject declaring productivity loss (61 hours per employed participant). Productivity loss was reported by all individuals who developed PHN (n=11), with higher losses observed in this cohort (mean 159 hours). No individual who discontinued work during the follow-up period (n=11) did so because of HZ or PHN.[153] Other studies (n range: 70-154), with a follow-up of to six months, reported productivity loss by patients and carers. Productivity loss increased with duration and severity of the HZ episode.[154, 155] Across studies, the average number of work days lost per case of HZ was between 3.6 and 4.4 days.[153-155] There is substantial uncertainty associated with these data given the small study numbers and limited duration of follow-up.

A 2018 cross-sectional observational study that surveyed GPs in Ireland calculated the direct costs involved in the diagnosis and management of HZ and PHN in primary care in Ireland.[108] From 1,000 registered GPs who were contacted, the response rate was low (15%) although the authors described the sample as representative of the Irish GP workforce. The authors took a payer perspective to calculate estimates of the direct costs of treating HZ and PHN in primary care in Ireland, with societal costs considered outside of the scope of this study.[108] The mean per-case direct cost (medication and GP visits) of treating HZ and PHN in primary care was €195 (range €153 to €236) and €201 (range €140 to €313), respectively. Using the GP Sentinel Surveillance System data (estimated 10,776 cases of acute HZ), the authors calculated the combined annual direct costs of treating HZ and PHN in primary care as €2.3 million (range: €1.8 to €2.8 million).[108] Similar Irish data for secondary care were not identified.

Based on English Hospital Episode Statistics from 2004 to 2013, the average length of stay and cost of a hospital admission due to HZ were reported as 9.2 days and GBP£2,872 (2013/2014 tariffs).[110] The average number of HZ-associated hospital days per year was 41,780 days, and average annual costs were estimated at £13 million; the majority of the admissions occurred in those aged 60 years and older.[110] A 2019 study reported healthcare resource utilisation and costs associated with HZ in individuals with and without immunocompromised health status in England between 2000 and 2012.[156] Mean costs increased with age and were consistently higher in immunocompromised individuals compared with those without immunocompromising conditions, as summarised in Table 3.4. The mean healthcare costs were higher for individuals with PHN lasting up to 90 days compared with individuals with HZ only. When considering individuals with PHN lasting up to 365 days, mean healthcare costs increased to approximately four times that of individuals with HZ only.[156]

Table 3.4 Mean cost of healthcare resource utilisation by immunocompromised status and age in England from 2000 to 2012

Age group (years)	Mean cost (£)*					
	Overall HZ cases§		HZ only cases+		PHN only cases¥	
	IC group	non-IC group	C group	non-IC group	IC group	non-IC group
18 – 49	173	98	157	92	302	216
50 – 59	199	119	168	107	468	263
60 – 64	236	127	191	114	539	271
65 – 69	242	146	196	124	489	288
70 – 79	290	190	229	149	540	388
≥ 80	427	320	308	242	780	607

Key: HZ – herpes zoster; IC – immunocompromised; PHN – post-herpetic neuralgia
*£ based on 2013/2014 tariff date
§90 days post initial HZ onset
+ Individuals with HZ only and includes costs seven days before until 30 days post HZ onset
¥ Individuals with HZ and PHN and includes costs seven days before until 90 days post initial HZ onset
Source: Curran 2019(156)

Higher direct medical costs among patients aged 50 years and over with PHN compared with HZ during the period 2010 to 2014 were also reported in a 2018 cohort study from Germany.(128) The estimated mean cost per HZ patient was €156 from the healthcare system perspective and €311 from the societal perspective. PHN was recorded among 11.9% of the 513 patients enrolled with HZ, with estimated mean costs per patient of €371 from the healthcare system perspective and €630 from the societal perspective.(128) In addition, a 2023 publication reported on the burden of hospitalisations related to HZ in Spain between 2016 and 2019 using administrative data.(111) The authors reported a total of 27,642 hospitalisations during this period (17.74 hospitalisations per 100,000 inhabitants) with a median length of stay of seven days (IQR 4 to 13). The annual cost of hospitalisations for HZ was estimated at €35.7 million, with a mean cost per hospitalised patient of €5,172.(111)

3.10 Size of the target population

NIAC recommends HZ vaccination for two population groups: immunocompetent or general population adults and immunocompromised adults. (8) The number of people potentially eligible for vaccination are described by group in this section.

3.10.1 General adult population

NIAC recommends the immunisation of all adults aged 65 years and over with RZV to prevent HZ and post-herpetic neuralgia.(8) In the 2022 census, there were over 776,315 people aged 65 years and over.(157) This represents a 22% increase relative

to the 2016 census.[158] It is unlikely that there will be full uptake of the vaccine and a range of scenario are explored in the budget impact analysis (Chapter 6).

3.10.2 Immunocompromised adults

In February 2024, NIAC issued three separate recommendations with respect to immunocompromised adults:[8]

- NIAC recommends the immunisation of HSCT (haematopoietic stem cell transplantation) recipients, aged 18 years and over with RZV.
- NIAC recommends consideration of immunisation with RZV for patients aged 18 to 49 years with immunocompromising conditions including solid organ transplant recipients, those with haematological malignancies, and those with advanced or untreated HIV (CD4 count <200 cells/µl), in conjunction with their treating specialist.
- NIAC recommends the immunisation of adults with immunocompromising conditions aged 50 years and over with RZV.

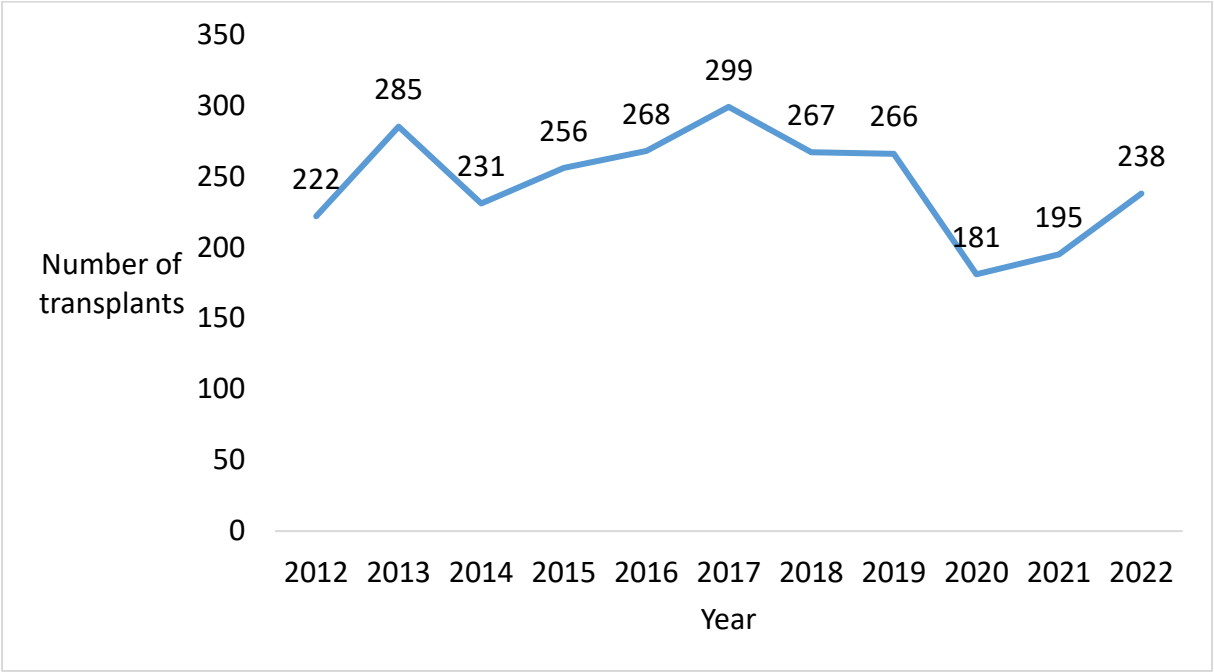
3.10.2.1 HSCT recipients aged 18 and over

The number of HSCT recipients (allogeneic and autologous) annually was estimated from EBMT registry data. The four Irish HSCT centres (Our Lady's Hospital of Sick Children in Crumlin, Dublin; St. Vincent's Hospital, Dublin; St. James's Hospital, Dublin; and Galway University Hospitals, Galway) submit annually to the registry. Data for Our Lady's Hospital in Crumlin were excluded from this analysis and data from the other three centres were assumed to be for those aged 18 and over. There was an average of 248 (range: 237 to 260) HSCT procedures carried out per annum in adult centres in the period 2016 to 2021.[159-164] St James's hospital has also been designated Ireland's National Adult chimeric antigen receptor (CAR) T-cell Centre, with the first patient treated in 2021. It is anticipated that an average of 50 patients a year will be treated at the centre.[165]

3.10.2.2 Solid organ transplant recipients aged 18-49

In Ireland, the HSE publishes an annual report on solid organ donation and transplant activity.[166] Considering the period 2013 to 2022, and excluding the years 2020 and 2021 in which the number of solid organ transplants appears lower due to the COVID-19 pandemic, there was an average of 259 (range: 222 to 311) solid organ transplants per year in Ireland (Figure 3.8). These data exclude paediatric kidney transplants; all other paediatric transplants are expected to be carried out in the UK.

Figure 3.8 Annual number of organ transplants in Ireland



Source: Organ Donation and Transplant Ireland Annual Reports[167-170]

3.10.2.3 Haematological malignancies

The National Cancer Registry of Ireland (NCRI) publishes the annual incidence of all cancers in Ireland. The mean number of cases of haematological malignancies in those aged 15 and over for 2018-2020 in Ireland was 2,366.[171] This estimate has been calculated from four NCRI classification groups: all leukaemia, all lymphomas, multiple myeloma, and other lymphoid and haematopoietic. There seems to be an upward trend in the incidence of haematological malignancies, particularly lymphoma cases, between 1996 and 2020. The reason for this is unclear; however, it may be related to better diagnostic accuracy and improved cancer registration as noted for the increase in overall rates of childhood cancer.[172]

Advanced or untreated HIV

The HSPC report the annual number of people diagnosed with HIV a year.[173] There are no national registry data in relation to the treatment status of those living with HIV or of the proportion that are virally suppressed. To determine the number of people with advanced or untreated HIV, a model from the European Centre for Disease Prevention and Control was identified.[174] This model predicted that in 2022 in Ireland, 7,200 people were living with HIV, of whom 6,500 were diagnosed, 5,700 were diagnosed and on treatment, and 5,400 of those on treatment were virally suppressed.[173] This would suggest that approximately 1,100 people are diagnosed with HIV and not virally supressed. This may act as an approximation of those considered to have advanced or untreated HIV.

3.10.2.4 Adults with immunocompromising conditions aged 50 years

In February 2024, NIAC recommended that RZV be considered for individuals with the following immunocompromising conditions: HSCT; solid organ transplant recipients; patients with cancer including solid tumours and haematological malignancies; patients with primary or acquired cellular and combined immune deficiencies resulting in lymphopenia; and patients with immune mediated inflammatory disorders who are receiving, have received, or are planned to receive immunosuppressive therapy.[8] The number of conditions which could be considered for this group is extensive, and without centralised data for all health service users, the absolute number of individuals to which these conditions would relate is difficult to estimate. To estimate the number of individuals in this group, data on individuals availing of two other adult vaccines who were identified as being in a medical at-risk category were extracted. In the first 52 weeks of COVID-19 vaccination (2021-2022,) 94,398 people aged 50 years and over declared themselves as immunocompromised at the time of vaccination.[175] In the 2022 to 2023 influenza vaccination season, 137,188 of those aged 50 and over who were vaccinated were reported to be in a high-risk medical category.[176] These figures may be indicative of the number of individuals who could be expected to fall within this NIAC recommendation group of adults with immunocompromising conditions aged 50 years and older and who would avail of vaccination.

3.11 Discussion

Primary infection with VZV, which typically occurs during childhood and presents as chickenpox, has been reported to result in approximately a 30% risk of a person developing HZ in their lifetime.[1] The risk of reactivation of the virus and subsequent HZ disease increases with age. HZ typically presents as an acute, painful, blistering rash. Complicated and chronic courses of the disease can occur, contributing severely to morbidity, most frequently in immunocompromised individuals.[3] As such, HZ represents a considerable burden to the health of affected individuals. It is important to note that the cohort of individuals at increased risk of HZ encompasses a range of underlying conditions, diseases and therapies, and there is no single definition of this cohort.

Increasing age and immunocompromised status are associated with higher incidence of HZ.[6, 94, 103, 105] The estimated number of HZ episodes in primary care in Ireland were derived from data obtained from the sentinel GP surveillance programme for HZ.[98] These data likely underestimate the total burden of HZ in the community, as they are limited to individuals who present to healthcare services. However, the data likely provide an estimate of the burden of HZ on GP practices in primary care. Data from 2013 to 2022 showed that those aged 75 to 79 years had the highest number

of episodes for HZ, with high levels also reported for those aged 70 to 74 years, 80 to 84 years and those aged 85 years and older. Considering the burden on secondary care services, HIPE data were used to examine hospital discharges with a primary and secondary diagnosis of HZ, as well mortality data.[109] Between 2013 and 2022, the overall mean number of annual patient discharges was relatively low. However, the mean number of annual patient discharges and the average length of stay were higher in older age groups. Overall, there were 54 deaths in acute hospitals where the person had a primary diagnosis of HZ between 2013 and 2022. Eighty-five percent of deaths were in those aged 75 years and over and almost half (46%) of all deaths occurred in those aged 84 years and over during this 10-year period. These data highlight the considerable burden experienced by patients due to HZ disease, as well as the significant care and cost burden placed on both primary care and acute hospital services in Ireland.

Post-herpetic neuralgia (PHN) is the most common complication of HZ. The proportion of people who develop PHN following onset of HZ is variable, with age playing a significant factor; those aged over 80 are twice as likely to develop PHN compared with those aged 50-59. Depending on the age at which a person develops HZ, as many as 5 to 10% of cases may experience symptoms of PHN lasting a year or more. As highlighted in this chapter, there are difficulties in quantifying the burden associated with HZ complications including PHN due to limitations in the available Irish data and inconsistent definitions used in international literature.

These data from Ireland align with international evidence reporting that HZ-associated hospitalisation rates increase with age and the majority of hospitalisations occur in adults aged 50 years and older.[6, 110, 111] Likewise, the association between increased age and higher mortality was reported in international literature.[6, 111, 142] Although mortality rates increase with increasing age, the overall HZ-related mortality rate in Europe is generally low.[142] However, it should be noted that the study authors reported that HZ mortality estimates varied considerably among countries. Similarly, the reliance on published evidence from other countries to supplement sections in this chapter in the absence of available data from Ireland should be considered a limitation. As such, caution should be applied when considering the applicability and comparability of international evidence to the Irish context.

No Irish data on the incidence of HZ in immunocompromised population were identified. International data show that there is an elevated risk of HZ in those with immunocompromising conditions, with the risk particularly high in those undergoing HSCT and solid organ transplants. The approximate population sizes for those most at risk from HZ were estimated from the best available data in this chapter. However, when there is no particular registry or reporting body for a condition,

these estimates are subject to considerable uncertainty. Furthermore, the available data on healthcare utilisation in Ireland did not differentiate between individuals in the general population and those that were immunocompromised or immunosuppressed. As such, it was not possible to determine the relative healthcare need in those at increased risk of HZ.

4 Clinical efficacy, effectiveness and safety

Key points

- A systematic review was undertaken of the clinical efficacy, effectiveness and safety of RZV for the prevention of HZ and associated complications, in adults aged 50 years and older and in adults aged 18 years and older who are at increased risk of HZ.
- Overall, 20 RCTs (n=47,414), 12 observational cohort studies (n=47,424,636), seven single-arm trials (n=10,230) and 11 single-arm observational studies (n≈546,416) were included. All of the RZV evidence presented in this review relates to Shingrix® as this was the only RZV vaccine licensed in Europe at the time of writing.
- Considering the efficacy and effectiveness of RZV in the general population aged 50 years and older:
    - Vaccine efficacy was estimated at 92% based on the combined RCT data (3.8 years follow-up), and 70% based on observational data (up to two years follow-up).
    - In the general population aged 50 years and over, there was evidence of waning effectiveness, with data from two RCTs with long-term follow-up indicating that efficacy reduced from an initial 97.7% at year one to 73.2% by year 10.
    - There was considerable uncertainty on the impact of age on efficacy and effectiveness due to limited data in age subgroups.
    - It is difficult to assess whether RZV vaccination prevents HZ-associated complications in individuals who develop breakthrough HZ due to limited data and inconsistency of the available data.
    - The evidence in regards to the impact that RZV vaccination has on the quality of life in those who develop HZ after vaccination is limited. However, there was a reduction in the severity of illness, burden of illness and the duration of clinically significant pain.
- For those at increased risk of HZ, vaccine efficacy was reported by two RCTs; efficacy was 68.2% in haematopoietic stem cell transplant recipients and 87.2% in those with haematological malignancies.
- Considering the safety of RZV:

  - RZV was more reactogenic than placebo; solicited local and systemic reactions were more frequent in vaccinated cohorts compared with placebo cohorts. RCT data suggest that the reactions are generally transient and mild to moderate in intensity; the most frequent reactions reported were pain at the reaction site, fatigue and myalgia.
  - The incidences of potential immune-mediated disease (pIMDs), serious adverse events (SAEs) and fatalities were similar in vaccine and placebo groups. One death was reported as vaccine-related in an individual with pre-existing thrombocytopenia.
  - RCT data suggest that adults who are at increased risk of HZ experience greater numbers of reactogenicity events, both local and systemic, post-RZV vaccination compared with placebo.
  - Rates of adverse events (AEs), SAEs and pIMDs in those who are at increased risk of HZ were similar in RZV and placebo arms; however, they varied by population. No deaths were recorded as related to the vaccine in this group.
- Searches for ongoing studies identified 37 ongoing trials that may present results relevant to the efficacy, effectiveness and safety of HZ vaccination. Most of the identified studies include the currently licensed RZV vaccine; however, trials of seven new compounds were also identified.
- The overall quality of RCTs, as judged by the ROB2 tool, was deemed at low risk of bias in half of trials. Overall quality of observational trials, as assessed using the ROBINS-I tool, was moderate risk of bias with one study at serious risk of bias.
- There is clear and consistent evidence that the RZV vaccine is effective at reducing HZ cases. Although RZV is initially effective, it is associated with waning immunity. The vaccine is effective in those considered at increased risk of HZ aged over 18 years, although effectiveness might be slightly lower in these populations than the adult general population aged over 50 years. While local and systemic AEs are common with RZV, SAEs are uncommon.

4.1 Introduction

The aim of this chapter is to review the clinical efficacy, effectiveness and safety of potential herpes zoster (HZ) vaccination strategies in adults aged 50 years and older and in adults aged 18 and older who are at increased risk of HZ.

4.2 Methods

A systematic review was undertaken of the clinical efficacy (a measure of how well vaccines work in a controlled trial),[177] effectiveness (a measure of how well vaccines work in the real world)[177] and safety of recombinant zoster vaccine (RZV) for the prevention of HZ and associated complications, in adults aged 50 years and older and in adults aged 18 years and older who are at increased risk of HZ.

4.2.1 Review protocol

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[178] and the protocol was registered with the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42023455731.

4.2.2 Research question

Two research questions were formulated to reflect the efficacy, effectiveness and safety outcomes associated with HZ vaccination:

- What is the clinical efficacy and effectiveness of currently licensed and approved RZV(s) for the prevention of HZ and associated complications, in adults aged 50 years and older and in adults aged 18 and older who are at increased risk of HZ?
- What is the safety profile of currently licensed and approved RZV(s) when used for the prevention of HZ in adults aged 50 years and older and in adults aged 18 and older who are at increased risk of HZ?

The PICOS (population, intervention, comparator, outcomes, and study design) framework used to formulate the review of clinical efficacy and effectiveness is presented in Table 4.1. The PICOS framework used to formulate the review of safety is presented in Table 4.2. The review of clinical efficacy focused on comparative studies only, whereas the review of safety also incorporated non-comparative studies.

Table 4.1 Clinical efficacy and effectiveness review inclusion and exclusion criteria

Criterion	Description
Population	Immunocompetent adults aged ≥ 50 years. Adults aged ≥ 18 years who are at increased risk of HZ, for example, immunocompromised individuals.
Intervention	Vaccination with a recombinant vaccine against HZ, approved and licensed for used within the European Union*: Zoster vaccine (recombinant, adjuvanted). (Studies that limit vaccine use to post-exposure prophylaxis will be excluded.)
Comparators	▪ vaccination with an alternative vaccine against HZ 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 HZ ▪ incidence of post-herpetic neuralgia (PHN) ▪ incidence of other complications associated with HZ including herpes zoster ophthalmicus (HZO) ▪ mortality associated with HZ ▪ hospitalisation associated with HZ ▪ 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: HZ - herpes zoster

Note: *The live, attenuated zoster vaccine Zostavax® was not included in this systematic review. In August 2023, Merck Sharp & Dohme informed HIQA that it had made the decision to voluntarily discontinue manufacturing and supplying the HZ vaccine, Zostavax® (zoster vaccine live); the proposed date for discontinuation is 31 July 2024.[19, 179]

Table 4.2 Safety review inclusion and exclusion criteria

Criterion	Description
Population	Immunocompetent adults aged ≥ 50 years Adults aged ≥ 18 years who are at increased risk of HZ, for example, immunocompromised individuals
Intervention	Vaccination with a recombinant vaccine against HZ, approved and licensed for used within the European Union: Zoster vaccine (recombinant, adjuvanted) (Studies that limit vaccine use to post-exposure prophylaxis will be excluded)
Comparators	▪ vaccination with an alternative vaccine against HZ 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 ▪ quasi-randomised controlled trials ▪ single arm trials ▪ non-randomised controlled trials ▪▪ quasi-experimental studies ▪▪ interrupted time series ▪▪ controlled before and after Observational studies with and without 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: HZ – herpes zoster

4.2.3 Search strategy and information sources

A comprehensive electronic search was performed in Embase (Elsevier), Medline (EBSCO) and the Cochrane Library. The search strings, developed in consultation with a librarian, are provided in Appendix A.1. A search for ongoing clinical trials relevant to the two research questions was also conducted in clinical trials registries. Searches were limited to the period from 2008 to July 2023. The first RZV received

marketing authorisation from the European Medicines Agency (EMA) in 2018 and therefore this date limit allowed for 10 years of data prior to marketing authorisation.

4.2.4 Study selection and data extraction

Titles and abstracts of articles retrieved were screened independently by two reviewers. The full text of potentially eligible articles was retrieved and independently assessed for eligibility by two reviewers according to the pre-specified inclusion and exclusion criteria outlined in Table 4.1 and Table 4.2. Data extraction was conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Any disagreements were resolved through discussion and with third party arbitration, when required.

4.2.5 Quality assessment

Two reviewers independently assessed the quality of included studies. Risk of bias was assessed using the Cochrane revised risk of bias tool for randomised controlled trials (RCTs) - RoB2.[180] Where relevant, the quality appraisal was conducted on the overall trial rather than the individual papers. The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the quality of non-randomised studies.[181] An adapted version of the Newcastle-Ottawa Quality Assessment Scale was used for the appraisal of non-comparative studies (see Appendix A.2).[182] Disagreements were resolved through discussion, or if necessary, involvement of a third reviewer.

4.2.6 Data synthesis and analysis

The reporting of this review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and national guidelines.[178, 183] Meta-analysis was undertaken in accordance with Cochrane methodology.[184] Data were presented separately for the general population and populations at increased risk of HZ.

Where studies were sufficiently homogenous in terms of participants, interventions and outcomes, meta-analysis was used to generate a combined effect estimate. Meta-analysis was conducted using the *meta* package in R version 4.3.1.[185] Clinical heterogeneity was assessed by reviewing inter-study variability in terms of the study population characteristics, study design, vaccine dose and schedule and outcome measurements. Results for both fixed effects and random effects meta-analyses were computed. Preference was given to random effects meta-analysis, due to heterogeneity in study populations and inclusion of real-world data. In cases where only two studies were available for a comparison, the fixed-effect estimate was used, as it was considered that there were insufficient data to support a reliable

estimate of between-study variance using a random-effects model. For random-effects models, the Knapp-Hartung adjustment was used to control for the uncertainty in estimates of the between-study heterogeneity.

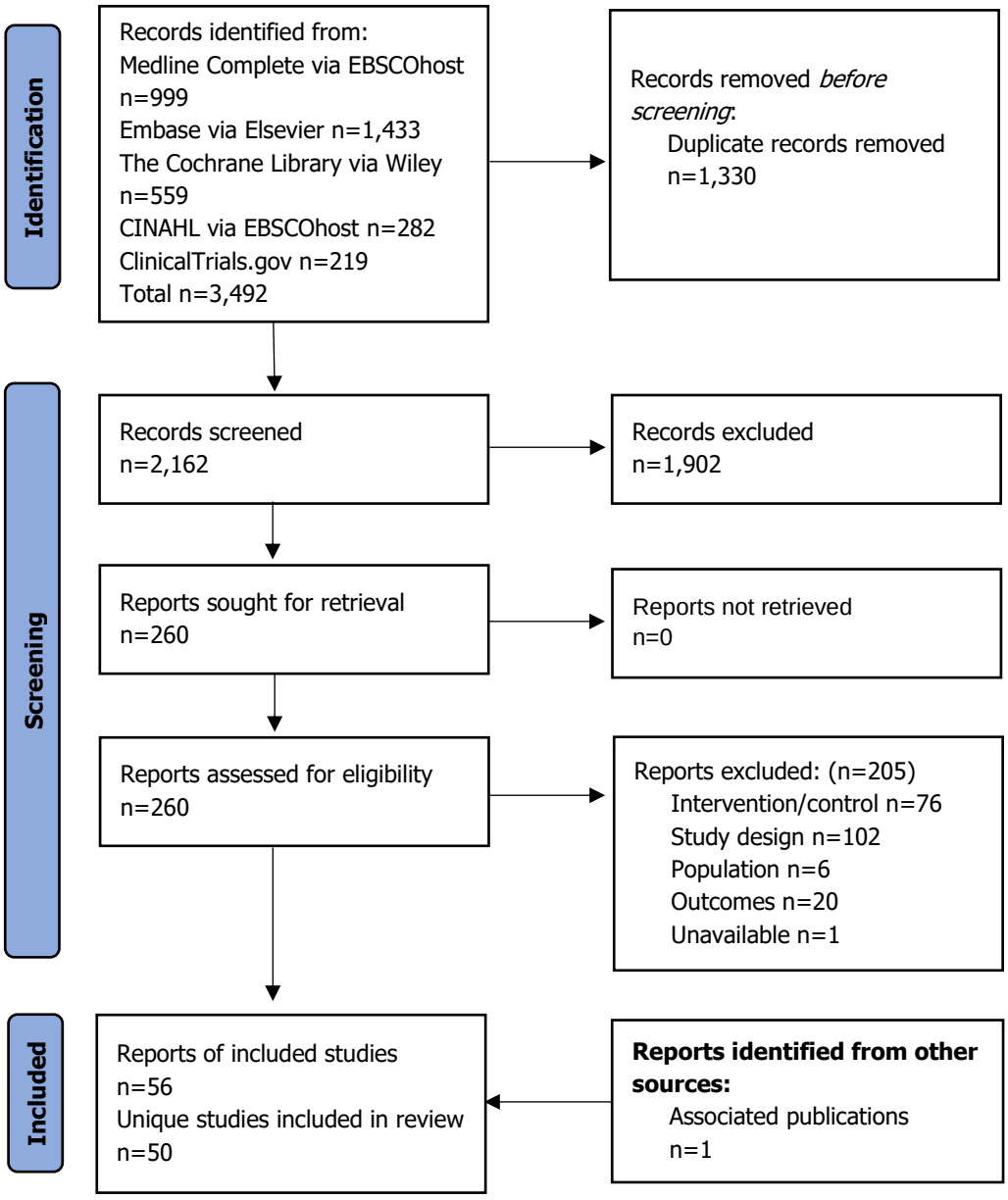
Statistical heterogeneity (a consequence of clinical or methodological heterogeneity) was assessed using the I^2 statistic, in line with Cochrane methodology.[186] The heterogeneity as measured by I^2 was considered in the context of the number of studies in the analysis, and the magnitude and direction of effect. Sensitivity analyses and subgroup analyses were used to assess the impact of potential sources of heterogeneity. Meta-regression was not considered as there were insufficient studies for such an analysis.

Relative risks were converted to vaccine efficacy to assist in interpretation of the results. Vaccine efficacy, as a percentage, was defined as 1 minus the incidence rate ratio (IRR) multiplied by 100.

4.3 Results

After removal of duplicates, 2,162 title and abstracts were assessed for eligibility. A total of 260 studies required full-text review with 56 studies fulfilling the inclusion criteria. At this point, studies were separated by outcome and are presented here as individual sections for efficacy, effectiveness, and safety. An overview of the study selection process is presented in Figure 4.1.

Figure 4.1 PRISMA flow diagram of study selection process



4.3.1 Characteristics of included studies

Fifty unique studies comprising 20 randomised control trials (RCTs, reported across 26 publications), 12 observational cohort studies, seven single-arm trials and 11 single-arm observational studies were included in this review (Table 4.3). All studies were published between 2013 and 2023. Three RCTs were carried out in the United States,[187-189] one in Belgium,[190] three across multiple European countries[191-193] and 13 across multiple countries worldwide.[194-207] Eighteen RCTs were conducted across multiple study centres[187, 188, 191-207] and two were single-centre RCTs.[190, 208] Twelve observational cohort studies included in this review were multicentre studies conducted in the United States,[209-219] while one was a single-centre study from

Sweden.[208] Three single-arm trials were conducted in the United States,[220-222] one in Canada[223] and one in multiple countries worldwide.[193] The study location was not provided for two of the single-arm trials.[224, 225] Eight of the single-arm observational studies were conducted in the United States,[226-233] one in Canada,[234] one in Italy[235] and one across multiple countries worldwide.[236]

The efficacy and safety of RZV against HZ in the general population was evaluated in two primary phase 3, randomised 1:1, observer blind, placebo-controlled multi-centre trials: the ZOE-50 trial[194] and the ZOE-70 trial.[195] One study reported the results of a long-term follow-up extension of both the ZOE-50 and ZOE-70 trials.[197] Six additional publications relating to the ZOE-50 and ZOE-70 trials were also included in this systematic review.[222, 237-241] Two of these studies examined quality of life (QoL) outcomes post RZV vaccination.[237, 241] For the observational cohort studies in the general population, seven evaluated clinical effectiveness[209, 210, 212-216] and four evaluated safety.[211, 217-219] The observational cohort studies included in this review measured how effective RZV was against HZ,[209, 210, 212-216] against PHN[214] and or against HZO.[209, 214, 216] Two studies examined the risk of developing Guillain-Barré syndrome (GBS) post RZV vaccination.[218, 219] Six single-arm trials[193, 220, 221, 223, 225, 242] and eight single arm observational studies included in this review evaluated the safety of RZV in the general population.[226, 227, 229, 231-233, 235, 236]

Fourteen RCTs[188, 194, 197-199, 204-206, 222, 238-241] limited their population to those aged 50 years and older, two RCTs[192, 198] limited it to those aged 60 years and older and one RCT[195] limited it to those aged 70 years and older. Only one RCT imposed an upper age limit with the study population restricted to those aged between 50 and 70 years of age.[190] In the observational cohort studies, nine studies reported on general populations aged 50 years and older,[209-213, 215-217, 219] two studies reported on those aged 65 years and older[214, 218] and one study reported on those aged 18 years and older. In the single-arm trials in the general population, three trials were limited to those aged 50 and older,[221, 223, 225] one trial to those aged 60 and older,[193] and two trials to those ages 65 and older.[220, 222] In the single-arm observational studies in the general population, five studies were limited to those aged 50 and older,[227, 229, 231, 233, 236] while three studies considered those aged 18 years and older.[226, 232, 235]

Clinical efficacy in the general population was informed by RCT data relating to 29,311 unique individuals,[194, 195] while observational studies provided effectiveness data for 43,990,671 unique individuals.[209, 210, 212-216] Safety in the general population was informed by RCT data for 30,790 unique individuals[191, 194, 195, 198, 199] and for 4,183 unique individuals in RCTs considering the co-administration of vaccines.[188-190, 204-206] Observational cohort studies provided safety data for 83,171 unique individuals.[208, 211, 217] Single-arm trials provided safety data for 10,114

unique individuals[193, 220-223, 225] while single-arm observational data were provided for over 31,351 unique individuals.[211, 217, 226, 227, 229, 232, 235] GBS-specific safety data were reported from 3,313,803 individuals.[218, 219, 231]

The efficacy and safety of RZV in immunocompromised patients were also evaluated in four phase 3 RCTs, one phase 2/3 RCT and two phase 1/2 RCTs. The patient groups evaluated were patients who underwent a hematopoietic stem cell transplant (HSCT),[187, 196, 207] patients with haematological malignancies,[200] renal transplants,[202] solid tumours[201] and patients with HIV.[203] The safety of co-administration of RZV with concomitant vaccines (pneumococcal, influenza, diphtheria-tetanus-acellular pertussis (Tdap), varicella zoster, mRNA-1273 COVID-19) was evaluated in six RCTs.[188-190, 204-206] One post-hoc analysis publication on combined data from both the ZOE-50 and ZOE-70 trials also reported disaggregated data for individuals who underwent a HSCT.[237] All RCTs relating to those at increased risk of HZ considered a population aged 18 years and older. One single-arm trial[224] and three single-arm observational studies limited their population to those at increased risk of HZ aged 18 years and older.[228, 230, 234] Clinical efficacy in the population at increased risk of HZ was informed by RCT data for 2,408 unique individuals.[196, 200] Safety in the population at increased risk of HZ was informed by RCT data for 3,178 unique individuals[187, 196, 200-203] and single-arm trial data for 116 individuals.[224]

Table 4.3 Characteristics of included publications

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
RCTs: General population								
ZOE-50 Lal, 2015[194]	18 Countries: Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Mexico, Spain, Sweden, Taiwan, UK, USA	Phase 3 RCT 1:1 randomised placebo-controlled	Adults ≥50 years ▪ Female: 61.2%	3.2 years	15,411	62.3 (9)	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ Safety
ZOE-70 Cunningham, 2016[195]	See Lal, 2015	Phase 3 RCT 1:1 randomised placebo-controlled	Adults ≥70 years ▪ Female: 54.9%	3.7 years	13,900	75.6 (4.7)	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ Safety
	See Lal, 2015	Combined ZOE-50 and ZOE-70	Adults ≥70 years ▪ Female: NR	3.8 years	17,531	NR	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ and PHN
(ZOE-50/70 pIMDs) Dagnew, 2021[222]	See Lal, 2015	Combined ZOE-50 and ZOE-70, post hoc analysis	Adults ≥50 years with pre-existing pIMDs ▪ Female: 60.4%	4.4 years	1,943	68.8 (9.6)	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ Safety
(ZOE-50/70 complications) Kovac, 2018[238]	See Lal, 2015	Combined ZOE-50 and ZOE-70	Adults ≥50 years ▪ Female: NR	ZOE-50: 3.2 years ZOE-70: 3.7 years	29,311	NR	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ complications (not PHN)

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
(ZOE-50/70 underlying conditions) Oostvogels, 2019[240]	See Lal, 2015	Combined ZOE-50 and ZOE-70 Post hoc analysis	Adults ≥50 and ≥70 years with existing comorbidities ▪ Female: 58.1%	NR	27,916	68.5 (9.8)	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ Safety
(ZOE-50/70 Frailty) Curran, 2021[239]	See Lal, 2015	Combined ZOE-50 and ZOE-70 Observational retrospective study	Adults ≥50 years assessed by frailty status ▪ Female: 58.1%	4 years	26,976	68.8	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ Safety
(ZOE-50/70 QoL) Curran, 2019b[241]	See Lal, 2015	Combined ZOE-50 and ZOE-70	Adults ≥50 years ▪ Female: NR	NR	ZOE-50: 14,751; ZOE-70: 16,593	NR	RZV versus placebo 2 doses (0 and 2 months)	HZ burden of illness and interference, QoL
ZOE-50/70 LTFU Strezova, 2022[197]	See Lal, 2015	Phase 3b extension ZOE-50 and ZOE-70	Adults ≥50 years ▪ Female: 60.7%	9.6 years	7,413	67.3 (9.4)	RZV versus historic control/placebo group in ZOE-50/70	Efficacy-HZ Safety
Zoster-026 Lal, 2018[199]	Estonia, USA	Phase 3 1:1:1 open label, randomised	Adults ≥50 and ≥70 years ▪ Female: 90%	1.8 years	354	64.5 (8.9)	RZV 2 doses (2 months apart)	Safety
Zoster-010 Chlibek, 2013[198]	Czech Republic, Spain, USA	Phase 2, observer blind, 4:4:2:1 randomised, multi-centre	Adults ≥50 years ▪ Female: 54%	1 year	410	65.0 (8.9)	RZV versus placebo (0 and 2 months)	Safety
Zoster-003 Chlibek, 2014[191]	Czech Republic, Germany, Sweden, Netherlands	Phase 2, single blind, randomised, multi-centre	Adults ≥60 years ▪ Female: NR	3 years	715	NR	RZV versus non-adjuvanted, 100 µgE/saline	Safety
Zoster-024 Chlibek, 2016[192]	Czech Republic, Germany, Sweden, Netherlands	Phase 2, open label, multi-centre	Adults ≥60 years ▪ Female: 60.5%	6 years	129	72.8 (4.96)	RZV (0 and 2 months)	Safety

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
RCTs: Population at increased risk of HZ								
ZOE-HSCT Bastidas, 2019[196]	28 countries: USA, UK, Spain, Greece, Finland, Belgium, Turkey, France, New Zealand, Canada, Germany, Italy, Korea, Japan, South Africa, Australia, Israel, Poland, Taiwan, Russia, Hong Kong, The Netherlands, Czech Republic, Bulgaria, Panama, Malaysia, South Korea	Phase 3 RCT 1:1 randomised placebo-controlled	Adults ≥18 years who had undergone recent autologous HSCT ▪ Female: 37.3%	1.9 years	1,846	54.8 (11.7)	RZV versus placebo 2 doses (0 and 2 months)	Efficacy-HZ Safety
ZOE-HSCT QoL Curran, 2019a[207]	See Bastidas, 2019	Phase 3 RCT 1:1 randomised placebo-controlled	Adults ≥18 years who had undergone recent autologous HSCT ▪ Female: 37.3%	1.9 years	1,721	56.0 (24-69)	RZV versus placebo 2 doses (0 and 2 months)	HZ burden of illness and interference, QoL
Zoster-039 Dagnew, 2019[200] *Haematological Malignancies*	21 countries: Australia, Belgium, Canada, the Czech Republic, Finland, France, Hong Kong, Italy, South Korea, New Zealand, Pakistan, Panama,	Phase 3 RCT 1:1 randomised placebo-controlled, multi-centre	Adults ≥18 years receiving cancer treatment ▪ Female: 40.6%	1.1 years	562	56.8 (15.5)	RZV versus placebo (0 and 1-2 months)	Efficacy-HZ Safety

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
	Poland, Russia, Singapore, Spain, Sweden, Taiwan, Turkey, UK, USA							
Zoster-028 Vink, 2019[201] *Solid Tumour*	Canada, Czech Republic, France, Republic of Korea, Spain, UK	Phase 2/3 RCT 1:1 randomised placebo-controlled	Adults ≥18 years receiving cancer treatment ▪ Female: RZV: 59.8%; placebo: 60.0%	1 year	262	57.1 (10.8)	RZV versus placebo (0 and 1-2 months)	Safety
Zoster-041 Vink, 2020[202] *Renal Transplant*	Belgium, Canada, Czech Republic, Finland, Italy, Panama, Republic of Korea, Spain, Taiwan	Phase 3 RCT 1:1 randomised placebo-controlled	Adult renal transplant recipients ≥18 years ▪ Female: 28.8%; placebo: 31.1%	1 year	264	RZV: 52.3 (12.5)	RZV versus placebo (0 and 1-2 months)	Safety
ID:110258 Stadtmauer, 2014[187] *HSCT*	USA	Phase 1/2a, randomised, observer blind, placebo-controlled, multi-centre	Adults ≥18 years who had undergone recent autologous HSCT ▪ Female: 40%	1.3 years	121	3 doses RZV: Median 56.5 (20-70)	RZV versus placebo (0 and 2 months)	Safety
Zoster-015 Berkowitz, 2015[203] *HIV*	Germany, USA, UK	Phase 1/2 RCT, randomised placebo-controlled multi-centre	HIV-infected adults ≥18 years ▪ Female: 5.7%	1.6 years	123	46 (10.93)	RZV versus placebo (0, 2 and 6 months)	Safety
ZOE-50/70/HSCT QoL Kim, 2022[237]		Combined ZOE-50/70/HSCT	Adults ≥18 years ▪ Female: ZOE-50: 61.2%; ZOE-70: 54.9%; ZOE-HSCT: 37.3%	ZOE-50: 146 days; ZOE-70: 628 days; ZOE-HSCT: 892 days	ZOE-50: 15,411; ZOE-70: 13,900; ZOE-HSCT: 1,846	NR	RZV versus placebo 2 doses (0 and 2 months)	QoL
RCTs: Co-administration with another vaccine								

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
Zoster-035 Marechal, 2019[204]	Estonia, Canada, USA	Phase 3, open label, 1:1 randomised multi-centre	Adults ≥50 years ▪ Female: 61.1%	1 year	865	63.2 (8.4)	PPV23 + RZV Co-Ad versus sequential administration	Safety
Zoster-059 Min, 2022[205]	Estonia, Canada, USA, Germany	Phase 3B, open label, 1:1 randomised, multi-centre	Adults ≥50 years ▪ Female: 57.7%	1 year	912	63.1	PCV13 + RZV Co-Ad versus sequential administration	Safety
Zoster-004 Schwarz, 2017[206]	Canada, Germany, USA	Phase 3, open label, 1:1 randomised, multi-centre	Adults ≥50 years ▪ Female: 51.1%	1.2 years	828	63.4 (8.3)	IIV4+ RZV Co-Ad versus sequential administration	Safety
ID: 109671, 109674 Leroux-Roels, 2012[190]	Belgium	Phase 1/2, open label, randomised, single centre	Adults 50-70 years ▪ Female: 62%	3.6 years	135	Means ranged from 55 to 57 years of age	RZV + OKA Co-Ad versus RZV 2 doses (0 and 2 months)	Safety
ID:116887 Strezova, 2019[188]	USA	Phase 3, 1:1 randomised, multi-centre	Adults ≥50 years ▪ Female: 53.9%	1 year	904	63.4 (8.4)	RZV + Tdap Co-Ad versus sequential administration	Safety
Naficy, 2023[189]	USA	Phase 3, 1:1 randomised, multi-centre	Adults ≥50 years ▪ Female: 56.4%	6 months	539	62.3 (8.6)	RZV + mRNA-1273 COVID-19 versus sequential administration	Safety
Single-arm trials								
Zoster-060 Hastie, 2021[193]	Czech Republic, Germany, Sweden	Phase 3B, open label, multi-centre	Adults ≥60 years Female: 64.5%	10 years	70	82.6 (4.4)	RZV (0 and 2 months)	Safety
Grupping, 2017[220]	USA	Phase 3, open label, group-matched study	Adults ≥65 years ▪ Female: 51.2%	3 months	430	70.9 (4.6)	N/A	Safety

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
Ocran-Appiah, 2021[225]	NR	Phase 3B, non-randomised, open-label study	Adults ≥50 years ▪ Female: 60.5%	12 months	8,687	72.6 (9.4)	N/A	Safety
Schmader, 2021[221]	USA	Phase 3 single-arm study	Adults ≥50 years Female: 58.6%	12 months	401	64.6	N/A	Safety
Godeaux, 2017[223]	Canada	Phase 3, non-randomised, open-label study	Adults ≥50 years ▪ Female: 65.6%	12 months	96	NR	N/A	Safety
Dagnew, 2021[222]	USA	Phase 3, open label study	Adults ≥65 years-vaccinated with RZV ▪ Female: HZ-PreVac: 51%; HZ-NonVac: 50.8%	12 months	430	NR	N/A	Safety
Pleyer, 2022[224]	NR	Prospective, open-label, phase 2 study	Adults ≥18 years-with chronic lymphocytic leukaemia immunocompromised ▪ Female: TN:41.1%; BTKi: 38%	7 days	116	Median: TN: 66.0; BTKi: 66.0	N/A	Safety
Observational cohort studies								
Bruxvoort, 2022[213]	USA	Retrospective observational cohort, multi-centre	Adults ≥50 years ▪ Female: 58.5%	2.6 years	41,251	Age split: 50-59: 14.3% 60-69: 36.9% 70-79: 36.3% ≥80: 12.5%	RZV with concomitant vaccination vs without	Effectiveness-HZ

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
Izurieta, 2021[214]	USA	Prospective observational cohort	Adults ≥65 years ▪ Female: 58.9%	2 doses: 7.1 months	15,589,546	2 dose: 74.1 (5.10)	RZV 1 or 2 dose versus unvaccinated	Effectiveness-HZ, HZO, PHN
Khan, 2022a[212]	USA	Retrospective cohort	Adults ≥50 years with IBD ▪ Female: 50-60: 18%; >60: 4%	2.1 years	33,300	2 dose: 50-60: 56.14 (2.98) >60: 72.95 (7.04)	Vaccinated 1 or 2 dose versus unvaccinated	Effectiveness-HZ
Kochhar, 2021[215]	USA	Retrospective observational cohort	Adults ≥50 years with IBD ▪ Female 53.2%	>9 months	18,672,820	Age split:50-65: 50.6%; >65 years: 49.4%	RZV 2 dose versus unvaccinated	Effectiveness-HZ
Lu, 2021[216]	USA	Retrospective observational cohort	Adults ≥50 years ▪ Female: 52.2%	2 years	4,842,579	Median: 65 (56-73 IQR)	RZV 2 dose versus unvaccinated	Effectiveness-HZO
Sun, 2021a[209]	USA	Retrospective observational cohort	Adults ≥50 years ▪ Female: 51.5%	2 years	78,356	Median: 61 (54-69 IQR)	RZV 2 dose versus unvaccinated	Effectiveness-HZ, HZO
Sun, 2021b[210]	USA	Retrospective observational cohort	Adults ≥50 years ▪ Female: 52.2%	Median: 7 months	4,769,819	Median 65 (56-73 IQR)	RZV 2 dose versus unvaccinated	Effectiveness-HZ
Goud, 2021[218]	USA	Retrospective observational cohort	Adults ≥65 years ▪ Female: 58.4%	42 days	2,666,496	74.8	RZV versus ZVL	Safety: GBS
Khan, 2022b[211]	USA	Retrospective cohort	Adults ≥50 years with IBD ▪ Female: 1%	90 days	3,354	72.86 (7.91)	RZV (0 and 2 month) vs unvaccinated	Safety
Leung, 2022[217]	USA	Retrospective observational cohort	Adults ≥50 years with IMIDs ▪ Female: IBM: 69%; CMS: 70%	42 days	IBM: 7,207 CMS: 72,468	IBM: Median 59 (55-62) CMS: Median 73 (70-78)	RZV vs unvaccinated	Safety

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
Nelson, 2022[219]	USA	Prospective, observational cohort study	Adults ≥50 years RZV, adults ≥60 years ZVL ▪ Female: 58%	2 years	RZV: 647,307 ZVL: 732,152	Age split: 50-59: 438,555 60-69: 1,107542 70-79: 651,366 ≥80: 268,256	RZV versus ZVL	Safety: GBS
VACCIMIL-Zoster Kallmark, 2023[208]	Sweden	Phase 4, non-randomised, single centre	Adults with RA ≥18 years receiving JAKi treatment for ≥3 months Female patients: 85.4%, controls: 72.5%	3.2 months	133	Median patients: 62 (53-71), controls: 61 (56-66)	RZV and JAKi treatment versus healthy controls all receiving RZV 2 doses (0 and 2 months)	Safety
Single-arm observational studies								
Raza, 2022[226]	USA	Retrospective observational	Adults ≥18 years with RA ▪ Female: 80.9%	NR	47	NR	N/A	Safety
Ackerson, 2021[227]	USA	Retrospective observational cohort study	Adults ≥50 years ▪ Female: dose 1: 57.5%; dose 2: 59%	9 months	31,120	NR	N/A	Safety
Barghash, 2020[228]	USA	Retrospective observational study	Adults ≥18 years Immunocompromised heart transplant patients ▪ Female: 35%	NR	65	66 (12.7)	N/A	Safety
Satyam, 2020[229]	USA	Prospective, observational study	Adults ≥50 years with IBD ▪ Female: 53.7%	Median: 207 days	67	NR	N/A	Safety
Venerito, 2023[235]	Italy	Prospective, observational study	Adults ≥18 years with RA	3 months	52	57.46 (11.64)	N/A	Safety

Study author, year	Country	Study Design	Population characteristics	Mean follow-up	Number of participants	Mean Age (SD)	Comparison	Outcome
			▪ Female: JAKi: 88.5%; bDMARDs: 80.8%					
Baumrin, 2021[230]	USA	Prospective, observational cohort study	Adults ≥18 years who had undergone recent allogenic HSCT ▪ Female: 42%	30 days	158	55.05 (13.83)	N/A	Safety
L'Huillier, 2021[234]	Canada	Prospective, interventional study	Adults ≥18 years-history of organ transplantation immunocompromised ▪ Female: 52.2%	3 months	23	Median: 38.0	N/A	Safety
Yih, 2022[231]	USA	Data mining study	Adults ≥50 years ▪ Female: NR	56 days	1,014,329 doses	NR	N/A	Safety
Gupta, 2022[232]	USA	Medical records review study	Adults ≥18 years with RA ▪ Female: 86.2%	3 months	65	Median: 68	N/A	Safety
Hesse, 2019[233]	USA	Descriptive analysis	Adults ≥50 years ▪ Female: 65.5%	8 months	4,381 reports	NR	N/A	Safety
Pirrotta, 2021[236]	Worldwide	Descriptive analysis	Adults ≥50 years ▪ Female: 59%	2 years 6 months	3,274 medical reports	N/A	N/A	Safety

Key: bDMARDs – biologic disease-modifying anti-rheumatic drugs; BTKi – Bruton's tyrosine kinase inhibitors; CMS – Centers for Medicare and Medicaid Services; Co-Ad – co-administration; GBS – Guillain-Barre syndrome; HIV – human immunodeficiency virus; HSCT – hematopoietic stem cell transplantation; HZ – herpes zoster; HZO – herpes zoster ophthalmicus; IBD – inflammatory bowel disease; IIV4 – quadrivalent seasonal inactivated influenza vaccine; IMID – immune-mediated inflammatory disease; IQR – interquartile range; JAKi – Janus Kinase inhibitors; LTFU – long-term follow-up; mRNA – messenger ribonucleic acid; N/A – not applicable; NR – not reported; OKA – VZV (Varicella Zoster Virus), Zostavax; PHN – post-herpetic neuralgia; pIMDs – potential immune-mediated diseases; PVC13 – 13-valent pneumococcal conjugate vaccine; PPV23 – 23-valent pneumococcal polysaccharide vaccine; QoL – quality of life; RCT – randomised control trial; RA – rheumatoid arthritis; RZV – recombinant zoster vaccine; SD – standard deviation; Tdap – diphtheria-tetanus-acellular pertussis vaccine; TN – treatment naïve.

4.3.2 Clinical efficacy/effectiveness of HZ vaccination in adults aged 50 years and older

4.3.2.1 Prevention of HZ

The efficacy and effectiveness of RZV in adults aged 50 years and older in the general population was reported in the ZOE-50, ZOE-70 and combined ZOE 50/70 RCTs[194, 195] and in four observational cohort studies,[209, 210, 212, 214] one of which was limited to a population with IBD.[212] These data are presented in Table 4.4. For all RCTs, the data extracted related to the modified vaccinated cohort, that is, a cohort which excluded participants who did not receive the second dose of RZV or placebo, or who had a confirmed episode of HZ within 30 days after the second dose.

The efficacy of the HZ vaccine, as measured by the number of HZ cases detected at follow-up in person-years, was also summarised through meta-analysis. All studies showed a statistically significant reduction in HZ cases following vaccination, but there was heterogeneity in the magnitude of effect. RCT evidence suggested a larger magnitude of effect than observed in the cohort studies. RCT and observational cohort studies were combined separately because of the identified heterogeneity.

In the two identified RCTs, the IRR for HZ cases was 0.08 (95% CI: 0.05 to 0.11), equating to a vaccine efficacy of 92% (Figure 4.2). There is considerable statistical heterogeneity in this estimate, which is likely due to differences in the study populations. The ZOE-50 trial included a general population aged 50 years and older (mean age 62.3 years), whereas the ZOE-70 trial included an over population aged 70 years and older (mean age 75.6 years). These data suggest there may be a difference in efficacy by age; this is further examined in subgroup analysis below. The IRR for HZ cases based on the observational cohort studies was 0.30 (95% confidence interval [CI]: 0.29 to 0.31) (Figure 4.3) corresponding to a vaccine effectiveness of 70%. There was no statistical heterogeneity in this estimate (I^2 = 0%). Sensitivity analysis was also undertaken whereby data specific to an immunocompromised population as reported by the Izurieta study were excluded.[214] Exclusion of this cohort did not impact the IRR.

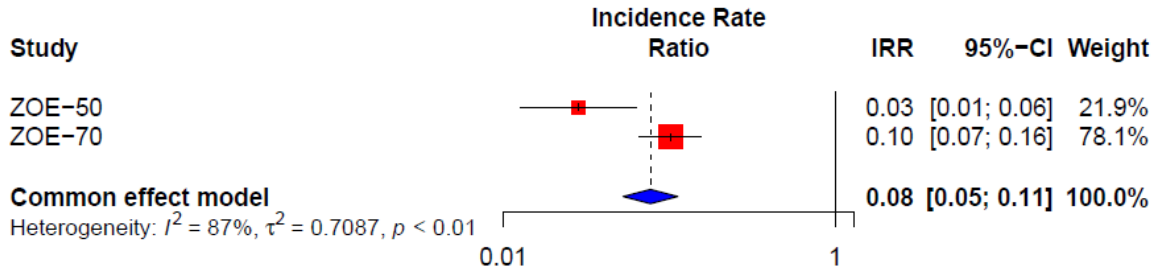
Table 4.4 Vaccine efficacy against HZ in the general population aged 50 years and older

Study author, year	Age	Mean follow up	Incidence rate of HZ (per 1,000 person years)		Efficacy % (95% CI)
			RZV (n/py)	Placebo (n/py)	
ZOE-50 Lal, 2015[194] n=15,411	≥50	3.2 years	0.3 (6/23297)	9.1 (210/23170.5)	97.2 (93.7-99.0)
	50-59		0.3 (3/11161.3)	7.8 (87/11134.7)	96.6 (89.6-99.3)
	60-69		0.3 (2/7007.9)	10.8 (75/6952.7)	97.4 (90.1-99.7)
	≥70		0.2 (1/5127.9)	9.4 (48/5083)	97.9 (87.9-100.0)
ZOE-70 Cunningham, 2016[195] n=13,900	≥70	3.7 years	0.9 (23/24405.1)	9.2 (223/24167.8)	89.8 (84.2-93.7)
	70-79		0.9 (17/19346.5)	8.8 (169/19247.5)	90.0 (83.5-94.4)
	≥80		1.2 (6/5058.5)	11 (54/4920.3)	89.1 (74.6-96.2)
ZOE-50/70 Combined Cunningham, 2016[195] n=17,531	≥70	3.8 years	0.8 (25/30725.5)	9.3 (284/30414.7)	91.3 (86.8-94.5)
	70-79		0.8 (19/24410.9)	8.9 (216/24262.8)	91.3 (86.0-94.9)
	≥80		1 (6/6314.6)	11.1 (68/6151.9)	91.4 (80.2-97.0)
Observational Cohort Studies			**RZV (n/py)**	**Unvaccinated (n/py)**	**Effectiveness % (HR) (95% CI)***
Izurieta, 2021[214] n=15,589,546	≥65	Median 7.1 months	3.09 (1,880/609)	10.3 (258,293/25,026)	70.1 (68.6-71.5)
	65-79		2.98 (1,473/495)	10.1 (191,424/18,962)	70.6 (68.9-72.1)
	≥80		3.57 (407/114)	11.0 (66869/6064)	68.5 (65.1-71.6)
Sun, 2021a[209] n=78,356	≥50	2 years	3.26 (27/8,291)	10.6 (1,273/119,719)	83.5 (74.9-89.2)
	50-59		0 (0/196)	9.4 (467/49,449)	100
	60-69		5.6 (4/717)	10.4 (442/42,592)	67.7 (11.8-88.1)
	70-79		2.9 (13/4,537)	11.9 (214/17,914)	83.3 (70.1-90.7)
	≥80		3.5 (10/2,841)	15.4 (150/9,764)	86.4 (73.5-93.0)
Sun, 2021b[210] n=4,769,819	≥50	Median: 7 months (2.8-13m IQR)	2.6 298/115,125)	8.9 (64,169/ 7,184,911)	85.5 (83.5-87.3)
	50-59		<5.5 (<11/2,019)	6.9 (15,424/2,252,215)	85.6 (53.3-95.6)
	60-69		>1.5 (>34/22,934)	8.5 (17,326/2,040,881)	87.7 (82.5-91.4)
	70-79		2.5 (161/65,423)	10.3 19,920/1,926,358)	86.5 (83.9-88.6)

	≥80		3.7 (92/24,750)	11.9 (11,499/965,456)	80.3 (75.1-84.3)
Khan, 2022a[212] n=33,300	50-60	2.1 years	0.0 (0/715.8)	3.9 (69/17,560.7)	100
	>60		1.8 (8/4444.9)	4.6 (268/58,663.2)	61 (20-81)

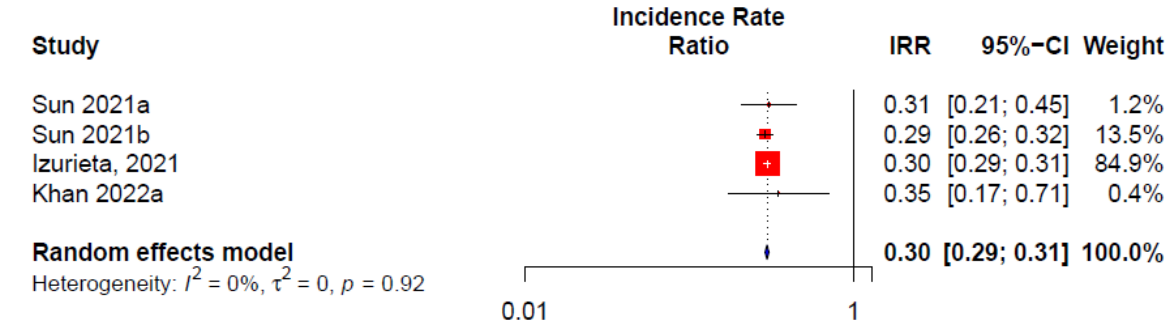
Key: CI – confidence interval; HR – hazard ratio; HZ – herpes zoster; IQR – interquartile range; n – number of herpes zoster cases; py – person years; RZV – recombinant zoster vaccine
Note: *Vaccine effectiveness was calculated as (1-Hazard Ratio) X 100%

Figure 4.2 Incidence of HZ in RCTs



Key: CI – confidence interval; HZ – herpes zoster; IRR – incidence rate ratio

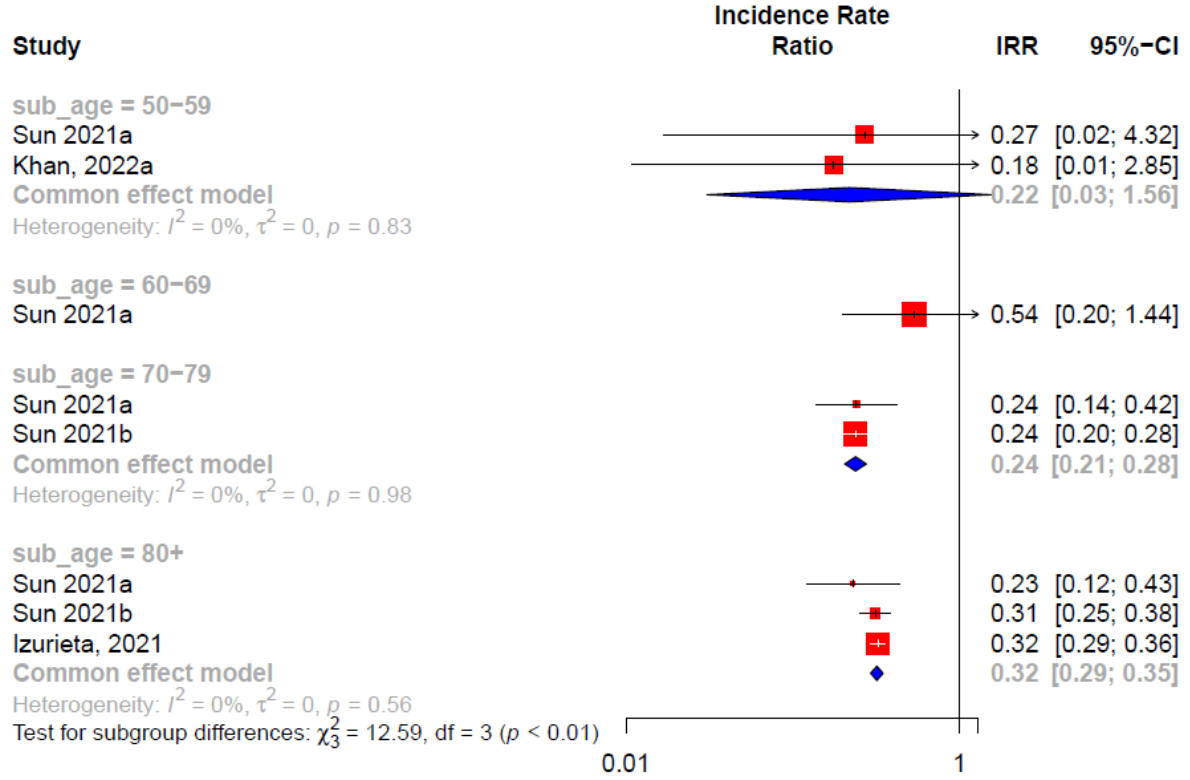
Figure 4.3 Incidence of HZ in observational cohort studies



Key: CI – confidence interval; HZ – herpes zoster; IRR – incidence rate ratio

A meta-analysis of HZ cases by 10-year age band was conducted (Figure 4.4). Only observational cohort evidence was considered in this analysis, as the RCT data were considered too disparate to pool in the same analysis. The test for differences in effectiveness suggests that there is a subgroup effect for vaccine effectiveness, with vaccine effectiveness decreasing with increasing age (p<0.01). Of note, estimates for the 60- to 69-years subgroup are based on only one study which appears to be an outlier. While a breakdown of cases by age was provided by one study (Sun, 2021b), these could not be included for the 50 to 59 or the 60 to 69 age groups as, due to low case numbers, precise counts were not provided in each group for data protection. Therefore, there is considerable uncertainty in this estimate due to limited data, and results should be interpreted with caution.

Figure 4.4 Meta-analysis of incidence of HZ by age

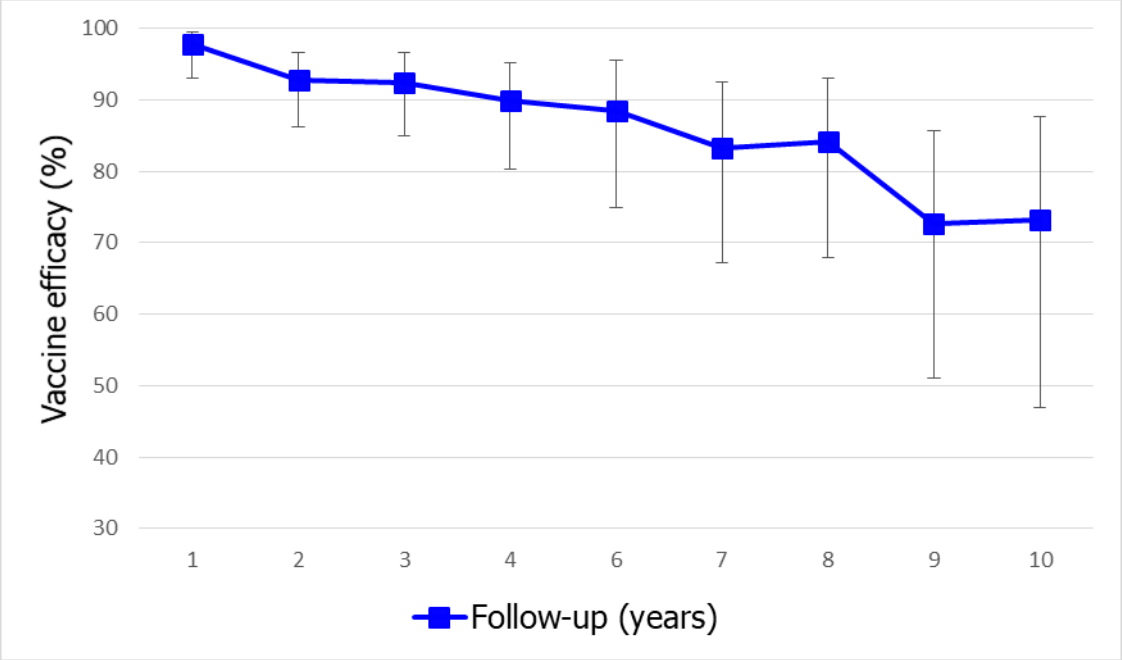


Key: CI – confidence interval; HZ – herpes zoster; IRR – incidence rate ratio
Note: A fixed effects model was used as there were insufficient data for a random effects model.
Sun, 2021b could not be included for the 50 to 59 or the 60 to 69 age groups as the incidence rates in the paper were masked due to low numbers of cases in each group.

The efficacy of RZV against HZ was evaluated in different cohorts by post-hoc analysis of the combined ZOE 50/70 trials data. Among participants with at least one pre-existing potential immune-mediated disease (pIMD), the overall vaccine efficacy was 90.5% (95% CI: 73.5-97.5),[222] ranging from 95.4% (95% CI: 89.0–98.5) in participants with one pre-existing selected medical condition to 90.9% (95% CI: 62.5–99.0) in those with six.[240] Amongst participants assessed by frailty status, vaccine efficacy was 90.2% (95% CI: 75.4-97.0) in those classified as frail compared with 95.8% (95% CI: 91.6-98.2) in non-frail participants.[239]

A long-term follow-up study of the ZOE-50/70 RCTs showed some waning efficacy over time, declining from 97.7% (95% CI: 93.1–99.5) at year one to 73.2% (95% CI: 46.9–87.6) at year 10 (Figure 4.5).[197]

Figure 4.5 Vaccine efficacy against HZ over time



Key: HZ – herpes zoster; LTFU – long term follow up
Note: Error bars are 95% confidence intervals. No data are available for year 5 because that period corresponds to the gap between ZOE-50 and ZOE-70 in the ZOE-LTFU study.
Source: Strezova *et al.*[197]

4.3.2.2 Prevention of post-herpetic neuralgia

Two studies, one RCT and one observational cohort study, examined the efficacy and effectiveness of RZV against post-herpetic neuralgia (PHN), the most common complication of HZ.[195, 214] These data are described both in the context of differences in the incidence of PHN across all individuals and secondly when just considering the incidence of PHN in the subset of individuals who developed HZ.

Based on the combined ZOE-50/70 trial data, for those aged 70 years and older (n=17,531), the incidence rate of PHN was estimated at 0.1 per 1,000 person-years in the vaccinated cohort compared with 1.2 per 1,000 person-years in the placebo cohort, corresponding to an adjusted vaccine efficacy of 88.8% (95% CI: 68.7 to 97.1).[195] The estimated vaccine efficacy for adults aged 50 years and older was 91.2% (95% CI: 75.9 to 97.7) and 71.2% (95% CI: 51.6 to 97.1) for those aged 80 years and older. There were no reports of PHN in any of the vaccinated participants aged 50 to 59 years or in those aged 60 to 69 years, therefore vaccine efficacy was reported as 100% for these age groups.[195]

The estimated vaccine effectiveness against PHN in an observational cohort study in adults 65 years and older was 76.6% (95% CI: 68.4 to 81.8).[214]

As noted, given that PHN is a complication of HZ, the risk of developing PHN was also estimated when considering just the subset of individuals with reported HZ. Estimates were informed by data reported in two combined RCTs[195] and one observational cohort study[214] (Table 4.5). In the combined RCT data, no difference in risk was observed (RR 1.30; 95% CI: 0.50 to 3.36). The much larger Izurieta, 2021 cohort study (n=15.6 million) identified a protective effect against PHN for those who had been vaccinated (RR 0.39, 95% CI 0.30 to 0.50).[214] Of note, PHN was defined differently in the studies; the ZOE 50/70 studies defined PHN as a worst pain score of three or more for pain that persisted or developed more than 90 days after the onset of HZ rash,[195] while Izurieta et al. defined PHN as occurring in the 90 to 180 days after HZ onset using an algorithm based on recorded relevant diagnostic codes and prescription data.[214]

Table 4.5 Risk of PHN following HZ

Study author, year	Age	PHN cases (n)	HZ cases (n)	Follow up	Relative risk (95% CI)
Combined ZOE 50/70 Cunningham, 2016[195] n=17,531	≥50	RZV=4 Placebo=46	RZV=29 Placebo=433*	Mean 3.8 years	1.30 (0.5-3.36)
Izurieta, 2021[214] n=15,589,546	≥65	RZV=55, Unvaccinated= 19,586	RZV=1,880, Unvaccinated= 258,293	Median 7.1 months	0.39 (0.30-0.50)

Key: CI – confidence interval; HZ – herpes zoster; PHN – post-herpetic neuralgia; RZV – recombinant zoster vaccine

4.3.2.3 Prevention of herpes zoster ophthalmicus

The effectiveness of RZV in preventing herpes zoster ophthalmicus (HZO) was examined in one RCT (ZOE-50/70 post hoc study)[238] and three observational cohort studies.[209, 214, 216] Where reported, these data are described both in the context of differences in the incidence of HZO across all individuals and secondly when just considering the subset of individuals who developed HZ.

A ZOE-50/70 post-hoc study (n=27,916) reported the incidence of HZO in the vaccinated and placebo cohorts aged 50 years and older.[238] One case of HZO (70 to 79 years) was reported in the vaccinated cohort compared with a total of seven cases in the placebo cohort (60 to 69 years: n=1; 70 to 79 years: n=4; ≥ 80 years: n=2).[238] When limited to the subset of cases with HZ, no difference in the risk of HZO was observed between the vaccinated and unvaccinated cohorts (Table 4.6)

Considering the observational data, vaccine effectiveness in preventing HZO was estimated at 66.8% (95% CI: 60.7–72.0) in a large observational cohort study (n=15.6 million) involving adults aged 65 years and older (incidence rate of HZO 0.3

per 1,000 person-years versus 0.8 per 1,000 person-years in the vaccinated and unvaccinated cohorts, respectively). No difference in vaccine effectiveness was observed when incidence in those aged 65 to 79 years was compared with that in those aged 80 years and older.[214] An observational cohort study (n=78,356) involving adults aged 50 years and older reported incidence rates of HZO of 0.12 cases versus 0.7 cases per 1,000 person-years in the vaccinated and unvaccinated cohorts, respectively, with an estimated overall adjusted vaccine effectiveness of 93.3% (95% CI: 48.7-99.1).[209] No estimate of effectiveness among age subgroups was calculated due to the small number of HZO cases.[209] In a third observational cohort study (n=4.8 million) involving those aged 50 years and older, the incidence rate of HZO was reported as 0.26 cases versus 0.77 cases per 1,000 person-years in the vaccinated and the unvaccinated cohorts, respectively, corresponding to an adjusted vaccine effectiveness of 89.1% (95% CI: 82.9-93.0).[216] This study reported that when stratified by age, effectiveness was similar across age groups.[216] The risk of developing HZO as a complication of HZ was calculated for two cohort studies (Table 4.6).[209, 214] A third cohort study, while reporting the number of HZO cases, did not report the number of HZ cases, so these data were not considered comparable.[216] The results of the analysis do not demonstrate that RZV reduces the risk of HZO as a complication of HZ.

Table 4.6 Risk of HZO as a complication of HZ

Study author, year	Age	HZO cases (n)	HZ cases (n)	Mean follow up	Relative risk (95% CI)
ZOE-50/70 complications Kovac, 2018[238] n=29,311	≥50	RZV=1 Placebo=7	RZV=32 Placebo=447*	3.8 years	2.00 (0.25-15.73)
Izurieta, 2021[214] n=15,589,546	≥65	RZV=157 Unvaccinated =19,306	RZV=1,880 Unvaccinated =258,293	Median 7.1 months	1.12 (0.96-1.30)
Sun, 2021a[209] n=78,356	≥50	RZV=1 Unvaccinated =87	RZV=27 Unvaccinated =1,273	2 years	0.54 (0.08-3.75)

Key: CI – confidence interval; HZ – herpes zoster; HZO – herpes zoster ophthalmicus; RZV – recombinant zoster vaccine

Note: *The number of HZ cases reported in the paper which also reported HZO cases was slightly different from the number of cases reported in Table 4.4 and Table 4.5. However, as the HZ case numbers from Kovac et al. are expected to be from the same data cut as the HZO cases, they were considered the most appropriate to use here.[238]

4.3.2.4 Prevention of other HZ complications and hospitalisation

Data relating to HZ-associated complications are described firstly in the context of the incidence of HZ-associated complications across all individuals and secondly when just considering the incidence of these complications in the subset of individuals who developed HZ. A post-hoc analysis of combined ZOE-50/70 data

(n=27,916) examined the efficacy of RZV against HZ-associated complications including PHN, HZ-associated vasculitis, stroke and disseminated, ophthalmic, neurologic and visceral diseases.[238] In the overall combined ZOE-50/70 population, HZO was the only HZ-associated complication recorded in the vaccinated cohort, with one case reported among the 32 participants with confirmed HZ.[238] Among placebo recipients, at least one HZ-related complication other than PHN was reported in 16 out of 477 recipients. Most HZ-related complications occurred in participants aged 70 years and older. No cases of HZ-associated visceral disease or stroke were recorded in the vaccine or placebo cohorts. No cases of disseminated disease, neurologic disease or HZ vasculitis was reported in the vaccine recipients. The rate of HZ complications increased with age for placebo recipients with 0.1 per 1,000 person-years in the 50-59 year old subgroup to 0.6 per 1,000 person-years in the subgroup aged 80 years or older.[238] Overall, vaccine efficacy against HZ-associated complications (excluding PHN) in adults aged 50 years or older was reported at 93.7% (95% CI: 59.5-99.9; p=0.0003), and 91.6% (95% CI: 43.3-99.8; p=0.0035) for adults aged 70 years or older. When PHN and other complications were considered together, HZ complications developed in 5 of the 32 vaccine recipients with confirmed HZ and 58 of the 477 placebo recipients. Vaccination with RZV resulted in a reduction in HZ complications, including PHN, of 91.3% (95% CI: 78.5–97.3; p< 0.0001) in adults aged 50 years or older and 88.6% (95% CI: 71.2-96.5; p< 0.0001) in adults aged 70 years or older.[238]

When considering specifically the cohort of individuals that developed HZ, the post-hoc analysis of combined ZOE-50/70 data reported the combined efficacy of RZV against a range of HZ-associated complications including PHN, HZ-associated vasculitis, stroke and disseminated, ophthalmic, neurologic and visceral diseases.[238] The risk of complications following HZ was similar in vaccinated and unvaccinated populations (Table 4.7 and Table 4.8).

Table 4.7 Risk of complications (excluding PHN) following HZ

Study author, year	Age	N complications	N HZ cases	Mean follow up	Relative risk (95% CI)
ZOE-50/70 complications Kovac, 2018[238] n=29,311	≥50	RZV=1, Placebo=16	RZV=32, Placebo=447*	3.8 years	0.93 (0.13-6.80)

Key: CI – confidence interval; HZ – herpes zoster; PHN – post-herpetic neuralgia; RZV – recombinant zoster vaccine

Note: *The number of HZ cases reported in the paper which also reported HZO cases was slightly different from the number of cases reported in Table 4.4 and Table 4.5. However, as the HZ case numbers from Kovac et al. are expected to be from the same data cut as the HZO cases, they were considered the most appropriate to use here.

Table 4.8 Risk of complications (including PHN) following HZ

Study author, year	Age	N complications	N HZ cases	Follow up	Relative risk (95% CI)
ZOE-50/70 complications Kovac, 2018[238] n=29,311	≥50	RZV=5, Placebo=58	RZV=32, Placebo=447*	3.8 years	1.29 (0.55-2.98)

Key: CI – confidence interval; HZ – herpes zoster; PHN – post-herpetic neuralgia; RZV – recombinant zoster vaccine

Note: *The number of HZ cases reported in the paper which also reported HZO cases was slightly different from the number of cases reported in Table 4.4 and Table 4.5. However, as the HZ case numbers from Kovac et al. are expected to be from the same data cut as the HZO cases, they were considered the most appropriate to use here.

In the ZOE-50 trial (n=15,411, 3.2 years mean follow-up), no deaths or hospitalisations as a result of HZ complications were reported. In the ZOE-70 trial (n=13,900, 3.7 years mean follow-up), while no hospitalisations related to HZ were reported in the vaccinated cohort, five HZ-related hospitalisations were reported in the placebo cohort. Of the five hospitalised as a result of HZ-related complications, two were as a result of neurologic disease, one due to disseminated HZ, one due to both neurologic and ophthalmic disease, and one due to a reaction to HZ pain-relief medication. The vaccine efficacy against HZ related mortality or hospitalisations was 100% (95% CI: -9.9-100.0; p=0.0636).[238]

4.3.3 Clinical efficacy and effectiveness of HZ vaccination in adults at increased risk of HZ

The clinical efficacy of RZV in preventing HZ in adults at increased risk of developing HZ was reported by two studies (Table 4.9): in adults with haematological malignancies,[200] and in adults who had undergone haematopoietic stem cell transplant (HSCT).[196]

In a large, multi-centre, observer-blind RCT in those aged 18 years and older with haematological malignancies receiving immunosuppressive cancer treatments (n=562), a vaccine efficacy of 87.2% was reported overall.[200] The ZOE-HSCT RCT, which was conducted in those aged 18 years and older who had recently undergone autologous HSCT (n=1,721), reported a clinical efficacy of 68.2% overall.[196] When stratified by age, vaccine efficacy was slightly higher in the 18 to 49 age group (72%) than in those aged 50 years and older (67%) based on IRRs of 0.28 and 0.33, respectively.[196]

Table 4.9 Vaccine efficacy against HZ in at-risk adults

Study author, year	Age	Follow up	Incidence rate of HZ (per 1,000 person years)		Efficacy % (95% CI)
			RZV (n/py)	Placebo (n/py)	
ZOE-HSCT Bastidas, 2019[196] n=1,846	≥18	1.8 years	30 (49/1633.1)	94.3 (135/1431.9)	68.2 (55.6-77.5)
	18-49		21.5 (9/419.4)	76 (29/381.4)	72* (39-88)
	≥50		33 (40/1213.7)	100.9 (106/1050.5)	67* (53-78)
Zoster-039 Dagnew, 2019[200] n=562	≥18	1 year	8.5 (2/NR)	66.2 (14/NR)	87.2 (44.3-98.6)

Key: CI – confidence interval; HZ – herpes zoster; n – number of HZ cases; py – person years; RZV – recombinant zoster vaccine; HSCT – haematopoietic stem cell transplantation; NR – not reported
Note: *calculated based on VE= (1-relative rate)*100

Only one RCT (n=1,846) reported vaccine efficacy against HZ complications in the increased risk group; the ZOE-HSCT study reported vaccine efficacy of RZV against HZ complications in the overall adult cohort of HSCT recipients.[196] Vaccine efficacy was approximately 89% (95% CI: 22-100; p=0.02) against PHN and 78% (95% CI: 19-96; p=0.02) against disseminated HZ.[196] RZV vaccination was also linked to a reduction in HZ-related hospitalisations with a hazard ratio (HR) of 0.15 (95% CI: 0.03-0.68) and a reduction in the duration of worst HZ pain (HR of 0.62, 95% CI: 0.42-0.89). Table 4.10 presents the data limited to the cohort of at-risk adults who have developed HZ. RZV vaccination appeared to reduce the relative risk of complications in those who developed HZ; however, none of these estimates were statistically significant.[196]

Table 4.10 Vaccine efficacy against HZ complications in at-risk adults following HZ

Study author, year	Age	Follow up	HZ complication cases (n)	HZ cases (n)	Relative risk (95% CI)
ZOE-HSCT Bastidas, 2019[196] n=1,846	≥18	1.8 years	**PHN**		
			RZV=1 Placebo=9	RZV=49 Placebo=135	0.31 (0.04- 2.35)
			disseminated HZ		
			RZV=3 Placebo=13	RZV=49 Placebo=135	0.64 (0.19-2.14)
			HZ-related hospitalisations		
			RZV=2 Placebo=13	RZV=49 Placebo=135	0.42 (0.10-1.81)

Key: CI – confidence interval; HZ – herpes zoster; HSCT – haematopoietic stem cell transplantation; PHN – post-herpetic neuralgia

4.3.4 Quality of life/patient-reported outcomes

Quality of life (QoL) scores as measured by validated QoL instruments, the EQ-5D and SF-36, were reported narratively in both the combined ZOE 50/70 data[241] and the ZOE-HSCT data.[207] Both studies reported a trend toward higher QoL scores (graphical presentation only) in RZV groups compared with placebo, but none reached statistical significance. Both studies also presented estimated mean pre-HZ utility scores, and utility losses for the period from day zero to week four in the placebo groups only, with the monthly utility loss associated with developing acute HZ estimated at 0.14 for the ZOE-50 trial and 0.13 for the combined population aged over 70 years from the ZOE-50 and ZOE-70 trials (see Appendix A, Table A2 and A3).

The Zoster Brief Pain Inventory (ZBPI) is a version of the Brief Pain Inventory that was specifically designed for use with patients who have or have had HZ. It provides a composite measure of intensity and duration of HZ pain[243] and was used in the ZOE-50 and ZOE-70 trials.[194, 195] Analysis of the ZOE-50 trial and combined ZOE-50/70 trials demonstrates a reduction in the ZBPI severity of illness score in those who progressed to develop HZ after RZV vaccination compared with placebo.[241] A reduction in ZBPI burden of illness score, which combines incidence of HZ with pain severity and duration in a single measure,[243] was also reported in the RZV cohort compared with the placebo cohort (see Table 4.11).[241] Further analysis of the same population also demonstrated a reduced ZBPI interference score after RZV vaccination compared with placebo (see Table 4.12). This is a measure of the degree that HZ pain affects activities of daily living (ADLs) in those who developed HZ.[241]

Table 4.11 HZ ZBPI severity and burden of illness (based on ZBPI Worst Pain) scores in the general population

Study author, year	Age	Follow up	RZV			Placebo		
			HZ cases	ZBPI Severity of Illness score	ZBPI Burden of Illness Score	HZ cases	ZBPI Severity of Illness score	ZBPI Burden of Illness Score
ZOE-50/70 QoL Curran, 2019b[241] n=ZOE-50: 14,751; ZOE-70: 16,593	ZOE-50: 50-59	NR	4	0.069	0.018	103	4.179	1.056
	ZOE-50: 60-69		3	0.082	0.020	89	4.274	1.067
	ZOE-50:≥ 70		2	0.069	0.019	60	6.059	1.644
	ZOE-50: ≥50		9	0.073	0.019	252	4.644	1.188
	Combined ZOE-70: 70-79		19	0.316	0.084	214	6.369	1.690
	Combined ZOE-70:≥ 80		6	1.222	0.344	67	6.777	1.932
	Combined ZOE-70:≥70		25	0.511	0.137	281	6.457	1.739

Key: NR – not reported; QoL – quality of life; RZV – recombinant zoster vaccine; ZBPI – Zoster Brief Pain Inventory

Table 4.12 HZ ZBPI interference (based on ZBPI ADL) scores in the general population

Study author, year	Age	Follow up	RZV			Placebo		
			HZ cases	ZBPI Severity of Interference score	ZBPI Burden of Interference Score	HZ cases	ZBPI Severity of Interference score	ZBPI Burden of Interference Score
ZOE-50/70 QoL Curran, 2019b[241] n=ZOE-50: 14,751;	ZOE-50: 50-59y	NR	4	0.024	0.006	103	2.850	0.720
	ZOE-50: 60-69		3	0.038	0.010	89	2.823	0.705
	ZOE-50:≥ 70		2	0.024	0.006	60	4.004	1.087
	ZOE-50: ≥50		9	0.028	0.007	252	3.110	0.796
	Combined ZOE-70: 70-79		19	0.180	0.048	214	4.261	1.130

Study author, year	Age	Follow up	RZV			Placebo		
			HZ cases	ZBPI Severity of Interference score	ZBPI Burden of Interference Score	HZ cases	ZBPI Severity of Interference score	ZBPI Burden of Interference Score
ZOE-70: 16,593	Combined ZOE-70:≥ 80		6	1.353	0.381	67	5.110	1.457
	Combined ZOE-70:≥70		25	0.434	0.116	281	4.443	1.196

Key: ADL – activities of daily living; HZ – herpes zoster; NR – not reported; QoL – quality of life; RZV – recombinant zoster vaccine; ZBPI – Zoster Brief Pain Inventory

Equivalent analyses carried out in an autologous HSCT cohort who developed HZ after either RZV vaccination or placebo highlighted a similar trend.[207] Reductions in ZBPI severity of illness score, ZBPI burden of illness score, ZBPI severity of interference and ZBPI burden of interference in RZV recipients compared with placebo recipients were seen in all age groups (see Table 4.13 and Table 4.14).[207]

Table 4.13 HZ ZBPI severity and burden of illness (based on ZBPI Worst Pain) in population at increased risk of HZ

Study author, year	Age	Follow up	RZV		Placebo	
			ZBPI Severity of Illness score	ZBPI Burden of Illness Score	ZBPI Severity of Illness score	ZBPI Burden of Illness Score
ZOE-HSCT Curran 2019a[207] n=1,721	18-49	21 months	3.779	1.911	20.769	11.544
	≥50		6.155	3.326	31.348	18.857
	Total		5.572	2.960	28.706	16.921

Key: HZ – herpes zoster; HSCT – hematopoietic stem cell transplantation; RZV – recombinant zoster vaccine; ZBPI – Zoster Brief Pain Inventory

Table 4.14 HZ ZBPI interference (based on ZBPI ADL) scores in population at increased risk of HZ

Study author, year	Age	Follow up	RZV		Placebo	
			ZBPI Severity of Interference score	ZBPI Burden of Interference Score	ZBPI Severity of Interference score	ZBPI Burden of Interference Score
ZOE-HSCT Curran 2019a[207] n=1,721	18-49	21 months	3.371	1.704	15.011	8.343
	≥50		3.908	2.112	21.355	12.846
	Total		3.776	2.007	19.770	11.654

Key: ADL – activities of daily living; HSCT – hematopoietic stem cell transplantation; RZV – recombinant zoster vaccine; ZBPI – Zoster Brief Pain Inventory

Consideration of the impact that RZV vaccination has in reducing the duration of clinically significant HZ-associated pain in those with confirmed HZ after RZV or placebo vaccination was assessed using data from the ZOE-50, ZOE-70 and ZOE-HSCT cohorts.[237] The mean difference in duration of clinically significant HZ-associated pain was 9.6 days in those 50 years and older, 13.9 days in those 70 years and older and 28.4 days in the autologous HSCT recipients (Table 4.15).[237] However, small sample sizes in the RZV groups limited analysis.

Table 4.15 Mean and median duration (in days) of clinically significant HZ associated pain and difference between the RZV and placebo groups.

Study author, year	Study	Follow up	RZV			Placebo			Placebo-RZV difference
			N	Duration (mean)	Median (min, max)	N	Duration (mean)	Median (min, max)	
ZOE-50/70/ HSCT QoL Kim, 2022[237]	ZOE-50 n=15,411	146 days	7	20.6 (26.8)	11.0 (3.0, 78.0)	221	30.2 (52.0)	15.0 (1.0, 464.0)	9.6
	ZOE-70 n=13,900	628 days	18	34.6 (45.5)	13.5 (1.0, 162.0)	198	48.5 (101.4)	19.0 (1.0, 834.0)	13.9
	ZOE-HSCT n=1,846	892 days	37	23.8 (31.9)	14.0 (1.0, 178.0)	120	52.2 (127.8)	24.0 (1.0, 1025.0)	28.4
	Total combined n=31,157	NR	62	26.6 (35.7)	12.5 (1.0, 178.0)	539	41.8 (92.6)	17.0 (1.0, 1025.0)	15.2

Key: HSCT – hematopoietic stem cell transplantation; N – number of participants with at least 1 confirmed HZ episode with clinically significant HZ-associated pain; NR – not reported; QoL – quality of life; RZV – recombinant zoster vaccine
Note: Clinically significant HZ-associated pain was based on ZBPI score ≥3 for worst pain.

4.3.5 Safety of HZ vaccination in adults aged 50 years and older

The safety of vaccinating with RZV in the general population, in the general population with co-morbidities, when co-administered with other vaccines, and in adults at increased risk of HZ is discussed separately in the following sections. Safety is considered in terms of reactogenicity, unsolicited adverse events (AEs) and serious adverse events (Grade 3+ AEs). An explanation of these terms as used in the included studies is provided below.

Reactogenicity refers to solicited local reactions, for example pain, redness or swelling at the reaction site; or systemic events, for example myalgia, fatigue, fever, headache and gastrointestinal complications that occur in the first seven days post vaccination.[194, 195, 197] An unsolicited AE is an untoward reaction during the first 30 days post vaccination or a solicited reaction that occurs outside the seven-day period.[194, 195, 197] Grade 3 AEs are AEs which prevented normal, everyday activities. AEs presented in the tables are any AEs that occurred within 30 days post vaccination; unsolicited AEs are specifically labelled. Grade 3+ AEs were considered serious adverse events (SAEs).

SAEs, potential immune-mediated diseases (pIMDs) and fatalities were generally reported over 12 months or the entire study period. Where details were provided in regards to events causally related to vaccination, these are presented. Results are discussed separately for RCTs, observational cohort studies, single-arm trials and single-arm observational studies. Due to heterogeneity in reporting, observational study results are reported narratively only.

4.3.5.1 Reactogenicity of RZV in the general population

Seven RCTs,[191, 192, 194, 195, 197-199] two observational cohort studies,[218, 219] two single-arm trials[221, 225] and five single-arm observational studies[227, 229, 231, 233, 236] reported on the reactogenicity and safety of RZV in the general population aged 50 years and older. Three single-arm observational studies reported reactogenicity and safety of RZV in individuals with rheumatoid arthritis aged 18 years and older (Table 4.16 and Table 4.17).[226, 232, 235]

In the RCTs, the rate of RZV recipients with any solicited local reaction — for example pain, redness or swelling at the reaction site — ranged from 74.1% to 84.0%, and the rate of recipients with Grade 3 local reactions ranged from 5.3% to 9.5%.[194, 195, 198] Solicited local reactions were reported in 7.9% to 11.9% of participants who received the placebo, with 0.0% to 0.4% of participants reporting Grade 3 local events (Table 4.16).[194, 195, 198] An observational cohort study reported a total of 202 medically-attended local AEs in the RZV group (n=647,307) compared with 96 events in the well-visit comparators (person who had an annual well-person healthcare visit) (n=1,806,260), with an adjusted relative risk of 2.75 (95% CI: 2.14-3.54).[219] Local reactions were reported in 74.6% to 92.3% of RZV recipients in the single-arm observational studies (data not in Table 4.16 due to heterogeneity of reporting).[229, 235] One observational study reported 74 events of local reactions from 810 cutaneous events voluntarily reported to an industry safety database.[236] A large single-arm observational study in the US (n=31,120) reported only local reactions which required medical attendance at 0.2% in RZV recipients.[227]

Systemic reactions — for example myalgia, fatigue, fever, headache and gastrointestinal complications — were reported more frequently after vaccination with RZV compared with placebo (Table 4.16). The rate of solicited systemic events after vaccination with RZV ranged from 53.0% to 66.1%, and Grade 3 events were reported in 6% to 11.4% of vaccine recipients.[194, 195, 198] In comparison, after vaccination with placebo, systemic events were reported in 18.4% to 29.5% of recipients, and 2% to 5.3% of recipients reported a Grade

3 systemic event.[194, 195, 198] One study recorded both local and systemic reactions together and found that 89.9% of RZV recipients reported a general reaction (either local or systemic) with 15.1% of RZV recipients reporting a Grade 3 local or systemic reaction.[199] Another study reported a total of 2,202 medically attended systemic events in the RZV group (n=647,307) compared with 2,795 events in the well-visit comparators (n=1,806,260), with an adjusted relative risk of 1.17 (95% CI: 1.10 to 1.24).[219] The rates of systemic reactions varied across the single-arm observational cohort studies. Two studies reported the rates as 56.7%[229] and 67.2%.[227] A third small study (n=65) reported a rate of 6.2%;[232] however, it is noted that this study was in a population aged 18 years and older.

Table 4.16 Reactogenicity in RCTs in general population aged 50 years and older

Study author, year	Follow up	Local/injection site reactions %, (95% CI)				Systemic reactions %, (95% CI)			
		Any local event		Grade 3 local event		Any systemic event		Grade 3 systemic event	
		RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	Placebo
ZOE-50 Lal, 2015[194]	3.2 years	81.5 (80.3–82.6)	11.9 (11.0–12.9)	9.5 (8.7–10.4)	0.4 (0.2–0.6)	66.1 (64.7–67.6)	29.5 (28.2–30.9)	11.4 (10.5–12.4)	2.4 (2.0–2.9)
ZOE-70 Cunningham, 2016[195]	3.7 years	74.1 (70.0–77.8)	9.9 (7.4–12.8)	8.5 (6.2–11.3)	0.2 (0.0–1.1)	53.0 (48.5–57.4)	25.15 (21.4–29.2)	6.0 (4.1–8.4)	2.0 (1.0–3.6)
ZOE-50/70 LTFU Strezova, 2022[197]	NR	Overall local or systemic reactions not reported.							
Zoster-026 Lal, 2018[199]	1 year 2 months	89.9 (83.0; 94.7) (local or systemic)	NA	15.1 (9.2; 22.8) (local or systemic Grade 3)	NA	89.9 (83.0; 94.7) (local or systemic)	NA	15.1 (9.2; 22.8) (local or systemic Grade 3)	NA
Zoster-010 Chlibek, 2013[198]	1 year	84.0 (77.1-89.5)	7.9 (1.7-21.4)	5.3 (2.3-10.2)	0.0 (0-9.3)	63.3 (55.1-71.0)	18.4 (7.7-34.3)	8.7 (4.7-14.4)	5.3 (0.6-17.7)
Zoster-003 Chlibek, 2014[191]	3 years	Overall local or systemic reactions not reported.							
Zoster-024 Chlibek, 2016[192]	6 years	Overall local or systemic reactions not reported.							
Single Arm Trials									
Ocran-Appiah, 2021[225]	12 months	Overall local or systemic reactions not reported.							
Schmader, 2021[221]	12 months	Overall local or systemic reactions not reported.							

Key: CI – confidence interval; LTFU – long-term follow-up; NA – not applicable; NR – not reported; RZV – recombinant zoster vaccine

Note: RCTs and single arm trials only presented in table. Observational data reported narratively due to heterogeneity in reporting. Solicited reports of local and systemic reactions.

4.3.5.2 Safety of RZV in the general population

In the RCTs, solicited or unsolicited AEs were reported in 79% to 87.3% of RZV vaccine recipients, with Grade 3 AEs occurring in 9.3% to 17% of these vaccine recipients (Table 4.17).[194, 195, 198] Unsolicited events were reported in 22.7%, with Grade 3 unsolicited AEs reported in 3.4% of RZV vaccine recipients.[193, 199] In the ZOE-50 and ZOE-70 RCTs, SAEs were recorded in all participants for up to 12 months after the second dose. In both trials, similar rates of SAEs were reported in the RZV arm and the placebo arms.[194, 195] However, it is noted that SAEs were more common in both the intervention arm and the placebo arm of the ZOE-70 trial (16.6% vs 17.5%) compared with the ZOE-50 trial (9% vs 8.9%).[194, 195]

A total of 2,497 AEs from 647,307 RZV recipients were reported in an observational study. This was compared with 2,896 AEs that were reported in 1,806,260 well-visit comparators, with a relative risk of 1.27 (95% CI: 1.20-1.34).[219] In the two single-arm trials, unsolicited AEs were recorded in 37.2% to 59.6% of RZV recipients.[221, 225] Grade 3 unsolicited AEs were reported in 6.2% to 11.1% of RZV recipients, with 7.4% considered related to the vaccine.[225] SAEs were reported in 3.5% to 8.4% of RZV recipients.[221, 225] One single-arm observational study reported a lower AE rate of 6.4%, but this may have been related to small sample sizes (n=47) and the fact that study eligibility included participants aged 18 years and older.[226]

In two of the RCTs, pIMDs were reported in 1% to 1.3% of RZV recipients, and 1.3% to 1.4% of placebo recipients, respectively.[194, 195] Another RCT reported two cases of pIMDs; however, these were not considered vaccine related.[192] Two RCTs reported no pIMDs[193, 199] and the remaining three RCTs did not report on pIMDs.[191, 197, 198] Two single-arm trials reported pIMDs in 0.5% to 0.7% of participants,[221, 225] of which two pIMDs were considered related to the vaccine.[225] In the single-arm observational studies, pIMDs were deemed to occur in 0% to 8.5% of RZV recipients.[226, 231, 232, 235, 236]

Two observational studies investigated the safety of vaccinating with RZV in populations with pre-existing pIMDs.[211, 217] A self-controlled risk-interval design study reported the risk of flare-ups among individuals with pre-existing pIMDs in the US (n=216,199).[217] The study reported no statistically significant effect on flare-ups of pIMDs post vaccination in adults aged 50 to 64 years, or in adults aged 65 years and older after the first or second dose of RZV compared with a control period.[217] Another study examined the safety of RZV in a retrospective matched cohort of veterans with inflammatory bowel disease (IBD) in the US (n=1,677).[211] The odds of developing IBD flare-ups post RZV

vaccination was reported as 1.25 (95% CI 0.65-2.41), suggesting vaccination with RZV is not associated with the risk of a IBD flare-up.[211]

Three observational studies reported the safety of RZV vaccination in relation to the occurrence of Guillain-Barré syndrome (GBS) in general older adult populations.[218, 219, 231] One study used US Centers for Disease Control and Prevention real-world data to investigate the risk of GBS post vaccination with RZV.[219] Analyses comparing RZV to a 'well-visit' non-vaccinated cohort reported an adjusted relative risk of GBS of 0.92 (95% CI 0.34-2.52) post-RZV vaccination.[219] Another US-based observational study reported five confirmed cases of GBS in 1,014,329 doses in RZV recipients.[231] A self-controlled cases series analysis leveraging US Medicare claims data compared the risk window pre- and post-RZV vaccination in those who developed GBS.[218] This identified an increased risk of GBS post-vaccination compared with pre-vaccination with a rate ratio of 2.84 (95% CI: 1.53 to 5.27) for fully vaccinated recipients based on claims data. This risk was higher in first dose recipients with a rate ratio of 7.72 (95% CI: 3.39 to 17.60), than in second dose recipients at 0.22 (95% CI: 0.04 to 1.22) compared with pre-vaccination.[218]

The rate of fatalities was similar in vaccine and placebo recipients in both the ZOE-50 and ZOE-70 RCTs (Table 4.17).[194, 195] Fatalities were reported in 2.2% and 2.3% of RZV vaccine and placebo recipients in the ZOE-50 RCT[194] and in 6.1% and 6.6% of RZV and placebo recipients in the ZOE-70 RCT, with one death assessed as being related to the vaccine in a participant with pre-existing thrombocytopenia.[195] The ZOE-LTFU reported zero fatalities that were considered related to the vaccine with a follow-up period of 9.6 years.[197] Another RCT, with a follow-up of three years, reported 14 participant deaths as a result of an SAE.[191] Two deaths as a result of SAEs were reported in the follow-on study; however, in both cases, no SAEs were considered vaccine related.[191, 192] Another RCT, with follow-up of 12 months post vaccination, reported zero fatalities.[198] In the single-arm trials, fatalities were reported in 0.5% to 1.2% of vaccinated participants, with zero fatalities related to the vaccine.[221, 225] Fatalities were reported of up to 1.2% in single-arm observational studies, but none were deemed causally related to vaccination.

Table 4.17 Safety of RZV in RCTs general population aged 50 years and older

Study author, year	Follow up	Any AE %, (95% CI)		Grade 3 AEs %, (95% CI)		SAEs %, (95% CI)		pIMDs reported %, (95% CI)		All-cause death %, (95% CI)	
		RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	Placebo
ZOE-50 Lal, 2015[194]	3.2 years	84.4 † (83.3–85.5)	37.8 † (36.4–39.3)	17 † (15.9–18.2)	3.2 † (2.7–3.8)	9 (8.3–9.6)	8.9 (8.3–9.6)	1 (0.8–1.3)	1.3(1.0–1.5)	2.2 (1.9-2.5)	2.3(1.9-2.6)
ZOE-70 Cunningham, 2016[195]	3.7 years	79 † (75.2–82.5)	29.5 † (25.6–33.7)	11.9 † (9.2–15.0)	2 † (1.0–3.6)	16.6 (15.7–17.5)	17.5 (16.6–18.4)	1.3 (1.1–1.6)	1.4 (1.1–1.7)	6.1 (5.6–6.7) 0.01*ϒ	6.6 (6.0–7.2) 0*
Zoster-026 Lal, 2018[199]	1 year 2 months	22.7 (15.5-31.3) Unsolicited	NA	3.4 (0.9-8.4)	NA	4.2 0*	NA	0	NA	0.9 0*	NA
ZOE-50/70 LTFU Strezova, 2022[197]	9.6 years	NR	NR	NR	NR	0	0	NR	NR	0*	0
Zoster-010 Chlibek, 2013[198]	1 year	87.3 (80.9-92.2)	21.1 (9.6-37.3)	9.3 (5.2-15.2)	5.3 (0.6-17.7)	0	0	NR	NR	0	0
Zoster-003 Chlibek, 2014[191]	3 years	NR	NR	NR	NR	NR 0*	NR	NR	NR	4.8 0*	NR
Zoster-024 Chlibek, 2016[192]	6 years	NR	NA	NR	NA	2.3 0*	NA	1.6 0*	NA	1.6 0*	NA
Single-Arm Trials											
Ocran-Appiah, 2021[225]	1 year	59.6 50.9* unsolicited	NA	11.1 7.4*	NA	8.4 0.02*	NA	0.7	NA	1.2 0*	NA
Schmader, 2021[221]	12 months	31.7 unsolicited	NA	6.2	NA	3.5 0*	NA	0.5 0*	NA	0.5 0*	NA

Key: AE – adverse event; CI – confidence interval; LTFU – long term follow up; NA – not applicable; NR – not reported; pIMDs – potential immune-mediated diseases; RZV – recombinant zoster vaccine; SAE – serious adverse event

Note: †within 7 days; *denotes number related to vaccination; ϒ90-year-old participant with pre-existing thrombocytopenia had acute myeloid leukaemia diagnosed 75 days after the first dose of RZV and died from neutropenic sepsis 97 days after vaccination, without having received the second dose.
RCTs and single-arm trials only presented in table. Observational data reported narratively due to heterogeneity in reporting.

4.3.5.3 Reactogenicity and safety of RZV in the general population with co-morbidities

The reactogenicity and safety of RZV was evaluated in different cohorts by post-hoc analysis of the combined ZOE 50/70 trials data. These post-hoc analyses examined reactogenicity and safety of RZV based on frailty of the recipients,[239] in those with pre-existing pIMDs[222] and in those with one or more pre-existing medical conditions.[240] Among participants assessed by frailty status, solicited and unsolicited AEs occurred more often in non-frail recipients of RZV than frail recipients of RZV (Table A4 and A5 in Appendix A). Solicited local reactions were experienced in 84.7% of non-frail RZV vaccine recipients compared with 68.5% in those classified as frail; solicited local reactions were also more common in those classified as non-frail in the placebo arm of the trial (11.2% versus 3.2%). In the vaccine and placebo cohorts, the incidence of Grade 3 local events did not differ significantly between the frail and the non-frail cohorts.[239] Solicited systemic reactions were experienced by 68.2% of non-frail recipients of RZV and 50.8% of frail recipients of RZV compared with 27.4% and 32.9% in the same groups receiving placebo. Furthermore Grade 3 systemic events were more common in the RZV group, ranging from 9.4% to 12% depending on frailty status.[239] Unsolicited AEs occurred in 73.6% to 78.3% of RZV recipients depending on frailty status compared with 32.3% to 36.1% in the placebo group, with Grade 3 AEs occurring in 14.1% to 17.4% of RZV recipients depending on frailty status, compared with 1.8% to 5.1% in the placebo group.[239] Fatalities were more common in frail individuals compared with non-frail participants, in both vaccine and placebo groups, but no deaths were deemed causally related to the vaccine.[239]

Among participants with pre-existing pIMDs, 14.6% of RZV recipients experienced SAEs compared with 11.7% of placebo recipients.[222] Furthermore, fatalities occurred in 5.1% of RZV recipients with pre-existing pIMDs which was similar to placebo recipients at 6.6%.[201, 222] The safety of vaccination with RZV compared with placebo in participants with one or more pre-existing medical conditions demonstrated similar rates of SAEs, pIMDs and deaths, but the rate of events increased with higher number of medical conditions present at vaccination in both the vaccinated and placebo cohorts.[240] The rates of pIMDs was similar among vaccinated and placebo cohorts and no increase in the rate of pIMDs was seen as the number of pre-existing medical conditions increased. The rate of all-cause death was similar between vaccinated and placebo groups; however, the number of deaths reported increased with the increase in the number of pre-existing medical conditions present in participants in both vaccinated and placebo cohorts.

The safety of RZV was evaluated in RA patients who were receiving JAKi treatment, adults with no diagnosis of rheumatic disorders or other conditions requiring immunosuppressive treatment served as controls.[208] Among participants with RA, 77.6% reported any AEs compared with 80.0% of controls. Six patients (6.5%) had increased RA disease activity after vaccination. No deaths or SAEs were reported.[208]

4.3.5.4 Reactogenicity of RZV when co-administered with other vaccines

The reactogenicity of RZV vaccination when administered simultaneously (co-administered groups) with another vaccine or sequentially (RZV alone groups) was investigated by six trials (Table 4.18).[188-190, 204-206] Two studies compared co-administration of RZV with a vaccine against pneumococcal disease versus RZV alone.[204-206] One study investigated the co-administration of RZV with an influenza vaccine against RZV alone.[206] One study compared RZV administered alongside the Tdap vaccine against RZV alone.[188] One study investigated the co-administration of RZV with a booster dose of mRNA-1273 for COVID-19 against mRNA-1273 and RZV administered sequentially two weeks apart.[189] Four of these studies were followed up for one year and one for 6 months, and all included populations aged 50 years and older. One further study compared co-administration of RZV with the live attenuated varicella zoster virus vaccine (OKA) in both young and older adults, followed up over 3.5 years.[190]

Local reactions such as pain, redness or swelling at the injection site, were self-reported by participants for up to seven days in all six studies.[188-190, 204-206] The incidence of local reactions was high across all groups ranging from 79.3% to 90.4%, in the RZV co-administration groups compared with 72.3% to 87.4% in RZV alone.[188, 204-206] The occurrences of Grade 3 local reactions were higher in the co-administration groups (10% to 19.8%) compared with RZV alone groups (7.4% to 13.2%).[188, 204-206]

Similarly, there was little reported difference between the co-administration groups and the RZV alone groups for systemic reactions (for example myalgia, fatigue, headache, shivering, fever or gastrointestinal symptoms);[188, 190, 204-206] however, there was a significant difference between systemic reactions following co-administration of RZV with mRNA-1273 at 74.9% compared with RZV alone in the sequential group (54.2%).[189] The incidence of systemic events ranged from 60.9% to 77.3% in the co-administration groups compared with between 52.1% and 74.7% in the RZV alone group.[188, 189, 204-206] The highest rates of local or systemic reactions occurred in the RZV plus 23-valent pneumococcal polysaccharide vaccine (PPV23) trials (Table 4.18).

Table 4.18 Reactogenicity with co-administration of RZV with another vaccine

Study author, year	Co-Ad with	Follow up	Local/injection site reactions %				Systemic reactions %			
			Any local event		Grade 3 local event		Any systemic event		Grade 3 systemic event	
			RZV + Co-Ad	RZV alone	RZV +Co-Ad	RZV alone	RZV +Co-Ad	RZV alone	RZV + Co-Ad	RZV alone
Zoster- 035 Marechal, 2019[204]	PPV23	1 year	90.4	85.8	19.8	13.2	77.3	74.7	17.7	16.2
Zoster- 004 Schwarz, 2017[206]	IIV4	1 year	79.3	72.3	10	7.4	60.9	52.1	8.8	5.7
Zoster-059 Min, 2022[205]	PCV13	1 year	Overall local or systemic reactions not reported.							
ID:116887 Strezova, 2019[188]	Tdap	1 year	88	87.4	11.1	11.2	72.7	74.5	14.7	14.3
ID:109671 Leroux-Roels, 2012[190]	OKA	3.5 years	Overall local or systemic reactions not reported.							
Naficy, 2023[189]	mRNA-1273	6 months	Overall local reactions not reported.				74.9	54.2	Overall Grade 3 systemic events not reported.	

Key: Co-Ad – co-administration; IIV4 – quadrivalent seasonal inactivated influenza vaccine; NR – not reported; OKA – VZV (varicella zoster virus), zostavax; PVC13 – 13-valent pneumococcal conjugate vaccine; PPV23 – 23-valent pneumococcal polysaccharide vaccine; RZV – recombinant zoster vaccine; Tdap – diphtheria-tetanus-acellular pertussis vaccine; mRNA-1273 – messenger RNA coronavirus 2019 vaccine

4.3.5.5 Safety of RZV when co-administered with other vaccines

The safety of RZV when co-administered with another vaccine was reported by six studies (Table 4.19).[188-190, 204-206] All studies reported unsolicited AEs and Grade 3 AEs within 30 days of vaccination, with SAEs, pIMDs and fatalities reported up to study end. Unsolicited AEs occurred in between 21.2% and 46.1% of co-administration recipients compared with between 23.1% and 41.5%[188, 189, 204-206] of those receiving RZV alone. Grade 3 unsolicited AEs were experienced by between 0% to 3.7% of vaccine co-administration recipients, compared with between 2.6% and 6.7% in the RZV alone groups.[188-190, 204-206] Over the entire study period, SAEs, pIMDs and fatalities occurred at similar rates irrespective of co-administration or RZV alone. Across the trials, the rates of SAEs were reported as ranging from 0% to 15.3% in the co-administration groups compared with between 0% and 14.5% in the RZV alone groups.[188-190, 204-206] The highest number of SAEs were reported in a trial that examined co-administration of RZV with a quadrivalent inactivated influenza vaccine (IIV4).[206] There was a low incidence of pIMDs, at 1% or less in all trials. No vaccine-related deaths were reported in any of these trials.

Table 4.19 Safety of RZV when co-administered with another vaccine

Study author, year	Co-Ad with	Follow up	Any AE %		Grade 3 AEs %		SAEs %		pIMDs reported %		All-cause death %	
			RZV + Co-Ad	RZV alone	RZV + Co-Ad	RZV alone	RZV + Co-Ad	RZV alone	RZV + Co-Ad	RZV alone	RZV + Co-Ad	RZV alone
Zoster-035 Marechal, 2019[204]	PPV23	1 year	30.6‡ (7.9%)*	32.3‡ (6.5%)*	3.7‡ (0.9%)*	6.5‡ (0.9%)*	3.5	3.9	0.2	0.2	0.5 0*	0.5 0*
Zoster-004 Schwarz, 2017[206]	IIV4	1 year	26.6‡	39‡	NR	NR	15.3 0*	14.5 0*	1	0.5	0.7 0*	1.2 0*
Zoster-059 Min, 2022[205]	PCV13	1 year	21.2‡ 7.8*	23.1‡ 5.4*	2‡ 0.7*	2.8‡ 0.6*	2.2 0*	2.2 0*	0.2 0*	0 0*	0.4 0*	0.6 0*
ID:116887 Strezova, 2019[188]	Tdap	1 year	25.5 6.6*	28.2‡ 7.4*	2.4‡ 0.5*	3.6‡ 0.5*	5.1 0*	7.4 0*	0	0	1 0*	1 0*
ID:109671 Leroux-Roels, 2012[190]	OKA	3.5 years	NR	NR	0	6.7‡	0	0	NR	NR	0	0
Naficy, 2023[189]	mRNA-1273 COVID-19	6 months	46.1 4.1*	41.5 4*	1.5%0*	2.6 <1*	2.2	1.8	<1	<1	0	0

Key: AE – adverse event; RZV – recombinant zoster vaccine; pIMDs – potential immune-mediated disease; Co-Ad – co-administration; IIV4 – quadrivalent seasonal inactivated influenza vaccine; NR – not reported; OKA – VZV (varicella zoster virus), zostavax; PVC13 – 13-valent pneumococcal conjugate vaccine; PPV23 – 23-valent pneumococcal polysaccharide vaccine; SAE – serious adverse event; Tdap – diphtheria-tetanus-acellular pertussis vaccine; mRNA-1273 – messenger RNA coronavirus 2019 vaccine

Note: *denotes number related to vaccination; ‡- within 30 days.

4.3.6 Additional safety studies

The reactogenicity and safety of two additional doses 10 years after primary vaccination with RZV were examined in one single-arm trial.[193] The results are reported here as they might be relevant if consideration is given to a booster dose or to providing the vaccine to people with prior vaccination. Pain was the most frequent local reaction, reported by 74.2% of RZV participants with Grade 3 pain reported by 3.2% of RZV recipients. Myalgia and fatigue were reported in 46.8% and 50% of RZV recipients, respectively. Grade 3 myalgia and fatigue were reported by 4.8% of participants. Unsolicited AEs were reported by 22.6% of participants of which five events were considered vaccine-related. SAEs were reported in seven participants, none of which were considered vaccine-related and none of which were fatal. No pIMDs were reported.[193]

Two single-arm trials reported the reactogenicity and safety of RZV in adults previously vaccinated with ZVL (n=882, follow-up 1 year 5 months).[220, 242] In one of these trials, local reactions were reported by 87.4% of participants in the HZ-NonVac cohort (participants who never received ZVL) and 89.8% in the HZ-PreVac cohort (participants who previously received ZVL over 5 years prior to study start). Grade 3 local reactions were reported as 9.8% in both cohorts. Systemic reactions were recorded as 72.0% in the HZ-NonVac cohort (Grade 3: 11.2%) and 69.3% in the HZ-PreVac cohort (Grade 3: 10.7%). Within 30 days after vaccination, 24.2% of participants in the HZ-NonVac group reported unsolicited AEs (2.3% Grade 3) and 36.3% of participants in the HZ-PreVac group (6.5% Grade 3). The reported rates of SAEs in both the HZ-NonVac and HZ-PreVac groups were the same at 1.9%; none were considered related to the vaccine by investigators. No deaths or pIMDs were reported. The other trial (n=430, 12 month follow-up) reported SAEs in 10.2% of the HZ-NonVac and 8.4% of the HZ-PreVac cohort.[242] Fatalities were reported in 1.4% of the HZ-NonVac cohort and 0.9% of the HZ-PreVac cohort. pIMDs were reported in 1.9% and 0.9% of the HZ-NonVac and HZ-PreVac cohorts, respectively. None of the SAEs, pIMDs or deaths reported were considered related to the vaccine. The two studies concluded that there are no clinically significant differences in reactogenicity and safety for RZV vaccination between those who have previously received ZVL vaccination and those who have never received ZVL.[220, 242]

One single-arm trial reported the safety of RZV in adults 50 years and older with a prior history of HZ (n=96, follow-up 12 months).[223] This trial reported that 77.9% of participants recorded local reactions and 71.6% systemic reactions. Solicited AEs were reported by 87.5% of participants with an HZ episode documented less than four years before study start, 66.7% in

participants with an episode documented between five to nine years before study start, and 69.2% in participants with an episode documented 10 years or more before study start. Unsolicited AEs and Grade 3 AEs reported were in line with other data on RZV vaccine recipients.[193, 199, 220, 221] This study concluded that RZV reactogenicity and safety are not impacted by a prior history of HZ.

4.3.7 Safety of HZ vaccination in adults at increased risk of HZ

4.3.7.1 Reactogenicity of RZV in adults at increased risk of HZ

The reactogenicity of RZV vaccination in at-risk adults groups was investigated in six RCTs,[187, 196, 200-203] one single-arm trial[224] (Table 4.20) and three single-arm observational studies.[228, 230, 234] Three of the at-risk populations included participants post autologous HSCT.[187, 196, 230] The other at-risk populations considered were adults with haematological malignancies,[200] solid tumours,[201] participants post-organ transplantation,[202, 228, 234] adults with chronic lymphocytic leukaemia[224, 244] and HIV-infected adults.[203]

Solicited local reactions, for example pain, redness or swelling at the injection site, were self-reported by participants for up to seven days in all 10 studies.[187, 196, 200-203, 224, 228, 230, 234, 244] The rate of solicited local reactions recorded in RCTs were similar in at-risk populations administered RZV vaccine ranging from 83.8%[200] to 87.1%[202] with lower rates reported in placebo recipients of between 6.4%[201] and 17.5%.[200] Grade 3 local reactions occurred in less than 0.3% in at-risk adults who received placebo vaccination,[196, 200-202] compared with rates of between 10.6%[202] and 14.2%[196] in those receiving RZV. One single-arm trial reported local reactions, with 97.4% experiencing any local event and 6% experiencing Grade 3 local events.[224] Of the single-arm observational studies, only one reported local reactions, with 87.3% of HSCT patients reporting any local event after RZV and 18.7% reporting Grade 3 local events.[230]

Systemic reactions for example myalgia, fatigue, headache, shivering, fever or gastrointestinal symptoms were reported by all 10 studies in at-risk populations.[187, 196, 200-203, 224, 228, 230, 234, 244] In the RCTs, the incidence of systemic events remained higher in at-risk adults receiving RZV vaccination with events occurring in between 68.2%[202] and 81.3%[201] of recipients compared with 48.9%[200] to 66.4%[201] of placebo recipients. Grade 3 systemic events were more common in RZV recipients ranging from events in 9.8%[202] to 22.3%[201] of those vaccinated compared with 6.1%[196] to 15.5%[201] in those given a placebo vaccine. One single-arm observational study reported local reactions, with 82.8% of HSCT patients reporting any local event after RZV and 26.5% reporting Grade 3 local events.[230]

Table 4.20 Reactogenicity in at-risk adult populations

Study author, year	Follow up	Local/injection site reactions				Systemic reactions			
		Any local event %		Grade 3 local event %		Any systemic event %		Grade 3 systemic event %	
		RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	Placebo
ZOE-HSCT Bastidas, 2019[196]	1.8 years	85.8	10.4	14.2	0.3	75.2	51	13.2	6.1
Zoster-039 Dagnew, 2019[200]	1 year	83.8	17.5	13.3	0	74.1	48.9	15.5	6.2
Zoster-028 Vink, 2019[201]	1 year	83.9	6.4	11.6	0	81.3	66.4	22.3	15.5
Zoster-041 Vink, 2020[202]	1 year	87.8	9.1	10.6	0	68.2	55.3	9.8	8.3
ID:110258 Stadtmauer, 2014[187]	1.3 years	Overall local or systemic reactions not reported.							
Zoster-015 Berkowitz, 2015[203]	1.5 years	Overall local or systemic reactions not reported.							
Single-arm trials									
Pleyer, 2022[224]	24 months	97.4	NA	6	NA	NR	NA	NR	NA

Key: HSCT – hematopoietic stem cell transplantation; NA – not applicable; NR – not reported; RZV – recombinant zoster vaccine

Note: Randomised-controlled trials and single-arm trials only presented in table. Observational data reported narratively due to heterogeneity in reporting.

4.3.7.2 Safety of RZV in adults at increased risk of HZ

The safety of RZV when administered in at-risk adult populations was reported by six RCTs[187, 196, 200-203], one single-arm trial[224, 228, 230, 234, 244] and three single-arm observational studies (Table 4.21).[228, 230, 234] All studies reported unsolicited AEs and Grade 3 AEs within 30 days of vaccination, with SAEs, pIMDs and fatalities reported up to study end.

Over the entire study period AEs, Grade 3 AEs, SAEs, pIMDs and fatalities mostly occurred at similar rates irrespective of the intervention, but rates varied across at-risk populations. Unsolicited AEs reported in RCTs[196, 200, 201, 203, 224, 228, 230, 244] ranged from 40% and 39.6% in the RZV and placebo arms, respectively, for a post-HSCT population[196] to 85.5% and 89.6% for the RZV and placebo arms, respectively, in those with solid tumours.[201] Grade 3 AEs in those receiving RZV vaccination[228] ranged from 1.7% in a post-HSCT population[187] to 16.4% in HIV-infected individuals[203] compared with a range of 3.8% in a post-renal transplantation population[202] to 13% in those with solid tumours.[201] Only two RCTs provided events that were considered related to RZV vaccination, reporting rates of 0.9% to 1.8% compared with no vaccination-related events in the placebo group.[200, 201] One single-arm trial reported AEs of 98.3% with Grade 3 AEs occurring in 14.7% of vaccinations in patients with chronic lymphocytic leukaemia; this study graded reactions on a scale of 1 to 5 and recorded no Grade 4 or Grade 5 reactions.[224] In the single-arm observational studies, high levels of AEs (92.1%) were reported in a HSCT population with 32.5% reporting Grade 3 AEs.[230] One single-arm observational study reported AEs in 29.2% of first doses and 28.3% of second doses in heart-transplant patients.[228]

In the RCTs, SAEs ranged from 8.1% and 4.1% in the RZV and placebo arms, respectively, in an HIV-infected population[203] to 35.7% and 26.7% in the RZV and placebo arms, respectively, in an HSCT population.[187] All seven RCTS reported if SAEs were related to vaccination, with similar numbers of vaccine-related SAEs occurring in RZV and placebo groups. One single-arm trial reported no SAE occurred with RZV vaccination.[224] Only one of the single-arm observational studies reported overall SAEs occurring in 1.3% of RZV vaccination recipients.[230]

The RCTs reported pIMDs in those receiving RZV vaccination[11, 19, 23-26, 52, 56] of less than 3% in at-risk populations compared to less than 1.5% in placebo group (Table 4.21). Only one study reported pIMDs deemed related to vaccination with 0.3% in the RZV group related compared with zero in the placebo group.[196] The single-arm trials did not report pIMDs. Two of the

single-arm observational studies reported that no pIMDs occurred in post-RZV participants.[230, 234] Five RCTs reported fatalities in both the intervention and placebo arms; however, none were deemed causally related to vaccination.[196, 200-203] The single-arm trials did not report fatalities, while the single-arm observational studies reported between 0.0%[228, 234] to 3.2%[230] fatalities, but reported none were related to vaccination.

Table 4.21 Safety of RZV in at-risk adult populations

Study author, year	Follow up	Any AE		Grade 3 AEs		SAEs without grade		pIMDs reported		Death	
		RZV %	Placebo %	RZV %	Placebo %	RZV %	Placebo %	RZV %	Placebo %	RZV %	Placebo %
ZOE-HSCT Bastidas, 2019[196]	1.8 years	29.0‡	38.2‡	6.5‡	5.1‡	28.5 3*	26.1 4*	1.4 3*	0.9 0*	8.4	8.5
Zoster-039 Dagnew, 2019[200]	1 year	47.3‡	45.9‡	8.8‡ 5[b]*	10‡ 0[b]*	23.3 1*	29.4 1*	1.1	0.7	10.2	13.3
Zoster-028 Vink, 2019[201]	1 year	85.5‡	89.6‡	15.4‡ 1[b]*	13‡ 0 [b]*	26.5 0*	28.7 0*	0	0.9	10.3 0*	9.6 0*
Zoster-041 Vink, 2020[202]	1 year	38.6	33.3	5.3‡	3.8	19.7 0*	25 1*	3	1.5	0.8 0*	0.8 0*
ID:110258 Stadtmauer, 2014[187]	1.3 years	75.9-83.3	51.6-70	1.7	0	35.7 1*	26.7 0*	0	0	NR	NR
Zoster-015 Berkowitz, 2015[203]	1.5 years	62.2‡	73.5‡	≤16.4‡	≤8.3‡	8.1 0*	4.1 0*	0	0	0	0
Single-arm trials											
Pleyer, 2022[224]	24 months	98.3	NA	14.7	NA	0	NA	NR	NA	NR	NA

Key: AE – adverse event; HSCT – hematopoietic stem cell transplantation; NA – not applicable; NR – not reported; RZV – recombinant zoster vaccine; pIMDs – potential immune-mediated disease; SAE – serious adverse event

Note: *denotes number related to vaccination; ‡ - within 30 days

Randomised controlled trials and single-arm trials only presented in table. Observational data reported narratively due to heterogeneity in reporting.

4.3.8 Ongoing trials

Searches for ongoing studies identified 37 ongoing trials that may present results relevant to the efficacy, effectiveness and safety of HZ vaccination. Most of the identified studies include the currently licensed RZV vaccine; however, trials of seven new compounds were also identified (CRV-101 vaccine, recombinant vaccine (LZ901), REC610, recombinant vaccine BV211, mRNA-1468, JCXH-105, VZV modRNA) (Table A6 in Appendix A).

4.4 Critical appraisal

Figure 4.6 presents a summary of the risk of bias assessment of the 20 RCTs included in this review. For the ZOE-50 and ZOE-70 trials, the quality appraisal was conducted on the overall trial rather than the individual papers.[222, 237-240] Similarly for the ZOE-HSCT trial, two papers were considered together to rate the quality of the overall trial.[196, 207]

No studies were identified to be at high risk of bias overall. Some overall concerns of risk of bias were identified for 11 studies,[187-190, 192, 198, 199, 204-206, 222, 238-241, 245] while nine studies were deemed to be at low risk of bias overall.[191, 194-197, 200-203] There were some concerns regarding risk of bias in measurement of the outcome in eight studies due to lack of blinding of outcome assessors.[188-190, 192, 199, 204-206] This included three open-label studies where participants were not blinded, but were required to self-report solicited AEs in a diary.[188, 189, 205, 206] Four studies did not blind outcome assessors[190, 192, 199, 204] and in three of those, outcome assessors subjectively decided on the causality of unsolicited and severe adverse effects.[190, 199, 204] In both scenarios, knowledge of the intervention may have influenced reporting or assessment of the outcome. There were some concerns for four studies regarding risk of bias due to deviations from the intended interventions.[188, 198, 205, 206] Risk of bias in selection of the reported result was found in the pooled ZOE-50/70 trial and two other studies (some concerns).[187, 190, 222, 237, 238, 240, 241, 246] Risk of bias related to the lack of publication of statistical analysis plans, or post-hoc analyses without any pre-specified plans. There were some concerns of risk of bias for one study regarding missing outcome data.[189] All studies were deemed at low risk in terms of bias arising from the randomisation process.

Figure 4.6 Risk of bias in RCTs

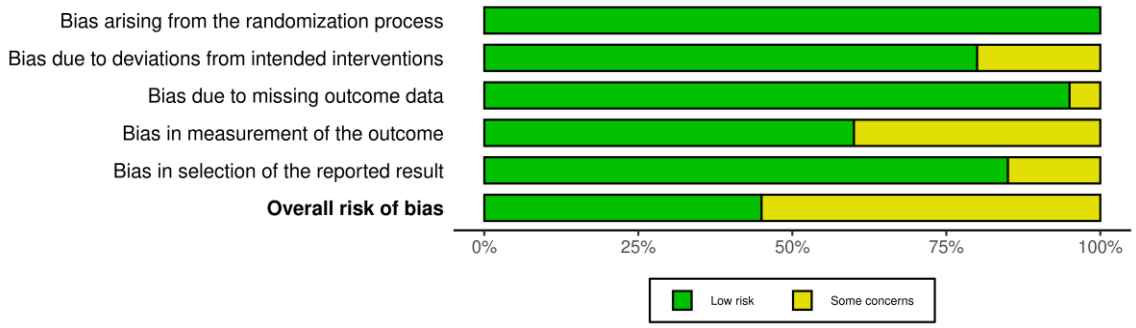


Figure 4.7 presents a summary of the risk of bias in the 12 non-randomised studies reviewed. Overall, 10 of the 12 studies were deemed at moderate risk of bias[209-214, 216-219] with two studies deemed at serious risk of bias.[208, 215] The domain deemed most at risk was bias due to confounding, due to the presence of confounding factors in all of the studies reviewed.[208-219] Ten studies appropriately adjusted for confounding through use of inverse probability weighting,[209, 210, 214, 216] self-control design to eliminate time-invariant confounders,[217, 218] use of time-varying adjustment alongside regression analyses[212, 213, 219] or matching.[211] Two studies were judged to be at serious risk of bias in this domain due to non-adjustment for confounding factors, such as health conditions or age.[208, 215] Risk of bias in selection of reported results was deemed moderate in 11 studies.[208-212, 214-217, 219] This was due to non-publication of protocols or pre-specified analyses plans, although all studies presented results of the analyses specified in the reported methods section. There was also risk of bias in selection of participants, with seven retrospective observational cohort studies deemed at moderate risk of bias.[209-211, 213-216] This was related to the use of an exclusion period for reporting outcomes for 30 days after the intervention when assessing the effectiveness of two doses of RZV. Although justified as allowing time for development of immune status after the second dose of RZV, it introduces the risk of immortal time bias compared to a target RCT with follow-up from vaccination. One study was considered to be at high risk of bias in relation to measurement of outcomes and selection of the reported results.[208] The remaining domains were all deemed at low risk of bias.

Figure 4.7 Risk of bias in non-randomised controlled trials

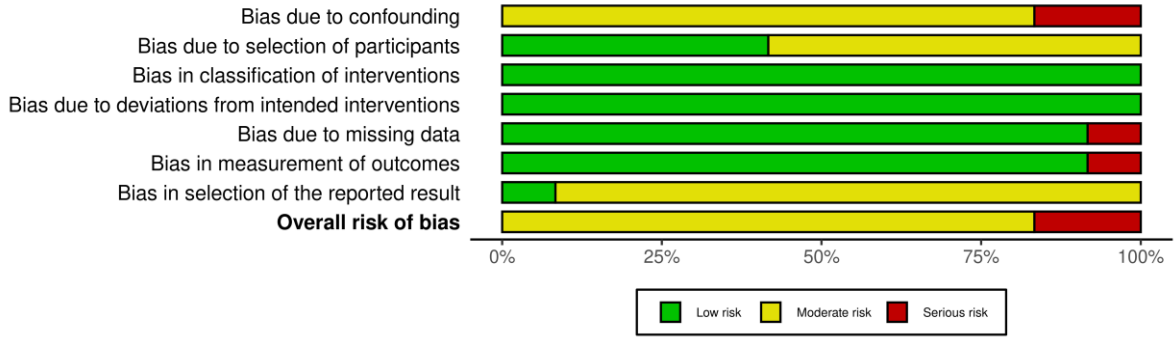


Table 4.22 presents a summary of the quality appraisal of each of the 18 single-arm studies reviewed. Overall, 14 studies were deemed to be of good quality[193, 220-223, 225, 227, 229-234, 236] with four studies judged to be poor quality.[224, 226, 228, 235] Of these, two studies were deemed poor quality due to the follow-up time for monitoring AEs either being too short[224, 235] while two studies did not report follow-up time.[226, 228] In studies where the follow-up time was considered to be too short, the follow-up for AE documentation was seven days. Given that the onset of AEs may occur after seven days, this timeframe was deemed inadequate. A follow-up time of approximately 30 days was reported in the other studies.

Table 4.22 Quality appraisal for single arm trials

	Selection			Comparability		Outcome			Quality
Study	**Representativeness of the exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Study controls for key confounders**	**Study controls for other factors**	**Assessment of outcome**	**Was follow up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	
Grupping, 2017[220]	★	★	★	★	★		★	★	Good
Raza, 2022[226]	★	★		★	★				Poor
Ocran-Appiah, 2021[225]	★	★		★	★			★	Good
Hesse, 2019[233]	★	★		★	★	★	★	★	Good
Schmader, 2021[221]	★	★		★	★		★	★	Good
Godeaux, 2017[223]	★	★	★	★	★	★	★	★	Good
Dagnew, 2020[242]	★	★	★	★			★	★	Good
Pirrotta, 2021[236]	★	★		★			★	★	Good
Baumrin, 2021[230]	★	★	★	★	★		★	★	Good
Venerito, 2023[235]	★	★		★	★			★	Poor
Satyam, 2020[229]	★	★		★	★		★	★	Good
L'Huillier, 2021[234]	★	★	★	★	★	★		★	Good
Ackerson, 2021[227]	★	★		★	★		★	★	Good
Barghash, 2020[228]				★	★	★		★	Poor
Yih, 2022[231]	★	★	★	★		★	★	★	Good
Pleyer, 2022[224]	★	★	★	★	★			★	Poor
Gupta, 2022[232]	★	★	★	★	★		★	★	Good
Hastie, 2021 [193]	★	★	★	★	★		★	★	Good

Note: ★ – stars are awarded for high-quality choices as deemed by the Newcastle Ottawa Scale, with one star available for each item in each category. To convert the Newcastle Ottawa Scale results to the AHRQ standards of good, fair or poor, for example, a 'good' result is based on three or four stars in the selection domain, one or two stars in the comparability domain and two or three stars in the outcome/exposure domain.

4.5 Discussion

A systematic review was undertaken to assess the clinical efficacy, effectiveness and safety of RZV for the prevention of HZ and associated complications in adults aged 50 years and older and in adults aged 18 and older who are at increased risk of HZ. Overall, 20 RCTs, 12 observational cohort studies, seven single-arm trials and 11 single-arm observational studies were identified for inclusion. All of the RZV evidence presented in this review relates to Shingrix® as this is the only RZV vaccine licensed in Europe at the time of writing.

4.5.1 Efficacy/effectiveness in preventing HZ

The efficacy and effectiveness of RZV in preventing HZ in adults aged 50 years and older in the general population was reported in the ZOE-50, ZOE-70 and combined ZOE-50/70 RCTs[194, 195] and in six observational cohort studies.[209, 210, 212-215]

A meta-analysis was undertaken to summarise efficacy of RZV vaccines as measured by the incidence of HZ cases. Observational data and RCT data were combined separately due to heterogeneity in outcome measures. Both analyses showed that RZV is effective in preventing HZ. Vaccine effectiveness according to observational data was estimated at 70%, whereas vaccine efficacy from combined RCT data was 92%. Our findings on the effectiveness of RZV align with those of a real-world study involving two million individuals, published in January 2024 (after our systematic searches were conducted), which reported RZV effectiveness at 79%.[247] While robust randomisation processes in RCTs ensure internal validity and allow causal inference, measuring the efficacy of a vaccine programme in a real-world setting permits the inclusion of heterogeneous populations where vaccine effects are unlikely to mirror the results from RCTs. The difference in vaccine efficacy between observational and RCT data may be related to methods of case identification. In the ZOE-50/70 clinical trials, all clinically suspected cases of HZ were PCR-confirmed or adjudicated by an expert panel. However, there is a risk that observational data may overestimate cases due to reliance on systems reporting and inability to verify cases.[214] For example, in observational studies such as Sun et al.,[209, 210] Izurieta et al.[214] and Kahn et al.,[212] identification relied on diagnosis codes and prescriptions observed in Medicare/insurance claims. Further differences may arise from heterogeneity in the age of participants across trials. The median age in observational studies was higher than the ZOE-50 trial in which 47% of the participants were aged 50-59, while the ZOE-70 trial was conducted in participants aged 70 and over. The impact of age on vaccine effectiveness was examined in the meta-analysis subgroup analysis, but results of that analysis are uncertain due to limited data. There is a slight trend toward decreasing efficacy with age; however,

additional evidence is needed, particularly in younger age groups — for example, 50 to 59 and 60 to 69 — to facilitate comparison across the age groups.

Factors such as age which may impact upon vaccine effectiveness must be carefully considered in planning vaccination programmes. If vaccine effectiveness decreases with age, there could be an opportunity to maximise on effectiveness by vaccinating at an earlier age. However, this would need to be balanced with the possibility of waning immunity. RCT data from long-term follow-up studies in the general population aged 50 years and over show that vaccine efficacy wanes from an initial 97.7% to 73.2% by year 10.[197] If waning were to follow a similar trend in the immunocompromised population aged 50 years and over, vaccine efficacy could potentially fall from 67% to approximately 50% within 10 years. A recent real-world study, published in January 2024, reported that RZV effectiveness waned from 79% to 73% over four years in the general population aged 50 years and older;[247] these data indicate similar rate of waning compared to that reported in the RCT long-term follow-up studies although based on short-term follow-up data (mean = 1.4 years).[197] Waning immunity may warrant consideration of a booster dose to prevent an age shift of HZ cases into older age cohorts where potential complications may be worse. At present (January 2024), none of the countries included in the overview of international practice offers a booster dose of RZV (see Chapter 2). Further research is required to clarify the rate of waning in other populations, and to investigate the effectiveness of booster doses. While there is also evidence that HZ affects males and females differently, with a higher incidence of HZ in females noted in systematic reviews,[248] none of the trials reviewed presented data separately by sex.

RCT data also indicate that co-morbidities may impact upon vaccine efficacy. Vaccine efficacy in persons with pIMDs was reported as 90.5% in the 50 years and over population and 86.2% in the 80 years and over population.[222] Vaccine efficacy was shown to decrease also with increasing numbers of co-morbidities from 95.4% with one medical condition to 90.5% with three or more medical conditions.[240] Frailty also was shown to affect vaccine efficacy, decreasing it from 95.8% in non-frail individuals to 90.2% in frail individuals.[239] Consideration should be given to the relationship between age and co-morbidities; Ireland has an ageing population demographic with an increasing life expectancy,[249] alongside which comes an increase in the number of people living with chronic conditions.

Vaccine efficacy in adults over the age of 18 who are deemed at increased risk of developing HZ was summarised in this systematic review. Vaccine efficacy was reported by two RCTs; efficacy was 68.2% in post-HSCT recipients[196] and 87.2% in those with haematological malignancies.[200] Vaccine efficacy varied greatly in the study populations at increased risk of HZ. There is substantial variation in the

baseline elevated risk of HZ across conditions as reported in Chapter 3, which could explain the differences in RZV efficacy in these different populations. The Summary of Product Characteristics for the licensed vaccine does not define what groups are included in the at 'increased risk' of HZ category,[21] and as noted in Chapter 2, there is considerable international variation in terms of the populations recommended for vaccination under the at 'increased risk' category. Therefore, consideration would need to be given to how such a recommendation could be implemented in Ireland.

4.5.1.1 Impact on severity of HZ disease and complications

Combined ZOE-50/70 trial data showed a vaccine efficacy for the prevention of PHN of 88.8%. This efficacy was calculated regardless of a case history of HZ. The efficacy in the observational study was 76.6%. Given that PHN develops after HZ, the risk of developing PHN was also calculated when limited to the subset of individuals that developed HZ. The RCT data indicated that the risk of developing PHN did not differ significantly between the vaccinated and placebo cohorts, suggesting the protection against developing PHN is due to the lower incidence of HZ. However, a protective effect against PHN was seen in the vaccinated cohort in the observational study (RR 0.39, 95% CI 0.3 to 0.5). This difference between the RCT and observational study data could be due to differences in the definition of PHN between studies, differences in the age range of the study populations (RCT: ≥ 50 years versus ≥65 years in the observational study). The effectiveness of RZV in preventing HZO ranged between 66.8% and 93.3% in observational studies regardless of a case history of HZ, with no difference in effectiveness observed across age subgroups. When considering just the subset of individuals who developed HZ, the included data suggest that RZV does not reduce the risk of HZO as a complication of HZ.

The risk of HZ complications including PHN, HZ-associated vasculitis, stroke and disseminated, ophthalmic, neurologic and visceral diseases was similar in vaccinated and unvaccinated populations. This suggests that RZV vaccination does not decrease the risk of HZ complications in those who develop breakthrough HZ; however, the data are limited by the small number of events. Data regarding the number of HZ-related hospitalisations were only available from two RCTs, and due to the low number of events in relation to participants, conclusions could not be made on this data. Larger data sets from observational studies are needed to show if RZV reduces HZ-related hospitalisations. Overall, it is difficult to assess whether RZV vaccination prevents HZ-associated complications in individuals who develop breakthrough HZ due to limited data and inconsistency of the data available at present.

4.5.2 Quality of life

The evidence in regards to the impact that RZV vaccination has on QoL in those who develop HZ after vaccination or placebo is limited. No statistically significant differences were seen in EQ-5D or SF-36 scores in RZV groups compared with placebo.[207, 241] Where utility scores for those in the placebo group who developed HZ were derived, the monthly utility loss of acute HZ was estimated at 0.14 for the ZOE-50 trial and 0.13 for the combined over-70 years of age population in the ZOE-50 and ZOE-70 trials. While this indicates the value of preventing HZ, the estimates were based on low numbers of HZ cases and therefore may not be representative. Results of the Zoster Brief Pain Inventory (ZBPI), a disease-specific instrument, reported reductions in severity of illness and burden of illness scores, with reduced interference of HZ in ADL in those who developed HZ post RZV vaccination compared to placebo, in both the general population and post-HSCT recipients, across all age-groups.[207, 241] Further analyses of the ZBPI data indicated a reduced duration of clinically significant HZ-associated pain in those who developed HZ after RZV compared to placebo vaccination. While small sample sizes limited interpretation of these results, reductions of 9.6 days, 13.9 days and 28.4 days were reported in the ZOE-50, ZOE-70 and ZOE-HSCT cohorts respectively. These duration data are limited to those with a severity of illness score greater than or equal to three, which is indicative of clinically significant pain. Overall, these results suggest that those who develop HZ after RZV vaccination have a less severe disease course that is of shorter duration compared with unvaccinated individuals with decreased interference with ADLs. However, small sample sizes, non-statistically significant results and use of disease-specific outcome measures indicate the need for further adequately powered, independent research using validated outcome measures to confirm results.

4.5.3 Safety of HZ vaccination

RZV was more reactogenic than the placebo; solicited local and systemic reactions were more frequent in the vaccinated cohorts compared with the placebo cohorts. RCT data based on the ZOE-50 and ZOE-70 trials suggest that the reactions are generally transient and mild to moderate in intensity; the most frequent reactions reported were pain at the reaction site, fatigue and myalgia. These trials reported that 95-96% of the recipients received two doses, suggesting that the reactogenicity of RZV did not greatly affect participants' willingness to receive the second dose.[194, 195] No evidence was found that pIMDs occurred more frequently in RZV recipients than among placebo recipients. The incidences of SAEs and fatalities were similar in vaccine and placebo groups;[194, 195] however, one death was reported as related to the vaccine in a participant with pre-existing thrombocytopenia.[194, 195] Similar reactogenicity and safety results were reported in the other RCTs;[191, 192, 198, 199] pain was the most frequently reported solicited local reaction, with fatigue and myalgia the most frequently reported solicited systemic reactions.[191, 198, 199] No SAEs were

considered related to the vaccine.[192, 197-199] No pIMDs or deaths were reported as vaccine-related in the other RCTs.[191, 192, 197-199]

No increase in reactogenicity with increasing frailty was observed[239] and the safety profile in terms of SAE occurrence was similar in the vaccine and placebo groups. The safety profile was similar in the vaccine and placebo groups in those participants with pre-existing pIMDs.[222]

Reactogenicity and safety results reported in the single-arm trials were also in line with the ZOE-50 and ZOE-70 trials.[221, 225] One single-arm trial that administered two additional doses 10 years after primary vaccination with RZV reported no safety concerns were identified,[193] and that the reactogenicity and safety profiles were similar to those identified in the ZOE-50 and ZOE-70 trials. The safety of RZV in participants who were previously vaccinated with ZVL was noted not to differ from that in ZVL-naïve RZV recipients, suggesting no safety concerns when considering the option to revaccinate prior ZVL recipients.[220, 222] One single-arm trial reported that RZV reactogenicity and safety are not impacted by a prior history of HZ.[223]

Three observational cohort studies reported the risk of GBS after RZV vaccination. One study reported a slightly increased risk of GBS in adults aged 65 years and older, resulting in an attributable risk of three per million RZV doses.[218] Another study reported uncertainty regarding potential associations with GBS, due to low incidence rates,[219] and a single-arm observational study did not find an association with GBS.[231] Overall, the data currently available do not indicate a causal relationship between RZV and GBS.

The reactogenicity and safety of RZV was reported when administered simultaneously with another vaccine (PPV23, PCV13, IIV4, Tdap, OKA, mRNA-1273 COVID-19) or sequentially.[188-190, 204-206] While local and systemic reactions were typically more common when co-administered with another vaccine, there was no clinically meaningful difference in the incidence of severe adverse events.

RCT data suggest that adults who are at increased risk of HZ experience greater numbers of reactogenicity events, both local and systemic, post RZV vaccination compared with placebo.[196, 200-202] This is also true for Grade 3 reactogenicity events. Single-arm studies and observational studies report similar incidences of events compared with RZV groups in RCTs. Rates of AEs, SAEs and pIMDs were similar in RZV and placebo arms; however, they varied by population. No deaths were recorded as related to the vaccine.

4.5.4 Quality of included studies

The overall quality of RCTs, as judged by the ROB2 tool, was deemed at low risk of bias in 50% of trials. Some concerns were raised about risk of bias in the other 50%

of RCTs, arising mainly from concerns over lack of blinding of outcome assessors which could influence reported outcomes. There were concerns also over non-reporting of certain aspects of the trials, including deviation from assigned interventions and lack of pre-specified statistical plans. Overall quality of observational trials, as assessed using the ROBINS-I tool, was moderate risk of bias, with two studies at serious risk of bias. Most bias arose from the presence of confounding factors in all studies reviewed, which all but one study adjusted for appropriately. Another risk of bias came from the use of an exclusion period for reporting outcomes for 30 days after interventions. Only one study published a pre-specified analysis plan; therefore, there exists a risk of bias in reported outcomes, albeit low, and all studies presented results as outlined in the reported methods section. Of the single-arm trials and observational studies, 5 of 18 were deemed poor quality, which was mostly due to inadequate follow-up monitoring for AEs, while the rest were deemed good quality.

A limitation of the quality appraisal for the included literature is the use of three different tools for quality appraisal that are not comparable. Caution must be employed in comparing outcomes from RCTs, observational and single-arm studies, as flaws inherent to their design affects the certainty of the evidence reported.

4.5.5 Strengths and limitations

There are several strengths and limitations to this systematic review. A comprehensive search strategy was employed which identified data 10 years prior to licensing of RZV by the European Medicines Agency. A broad range of study designs were also included in this systematic review, leading to a comprehensive overview of efficacy, effectiveness and safety of RZV.

Secondary analyses — including investigation of complications of HZ, and subgroup analyses by age — were limited by small sample size, leading to inconclusive results. In the primary analyses, differences by study design (RCT compared with observational cohort) were identified. However, for some analyses, only RCT data were available. Ideally in a systematic review, the effect of the intervention should be estimated by an intention-to-treat analysis that includes all randomised participants, irrespective of whether they received the intervention. However, the analysis was limited to the modified total vaccinated cohorts, as these were the only data available. As a consequence, the analysis was based on individuals who received both scheduled doses of the vaccine. The extent to which this may bias estimates of efficacy depends on uptake of the full schedule. In Ireland, completion of multiple-dose vaccinations is typically high.

Our findings on the effectiveness and safety of HZ vaccines in the general population align with those of a recent Cochrane systematic review.[250] The Cochrane authors

concluded that the vaccinated group exhibited a significant reduction in cumulative HZ incidence and that RZV may be deemed safe, as no notable differences in serious adverse events were observed between the vaccinated and placebo groups. Nevertheless, it is important to acknowledge certain limitations within this review. The evaluation of RZV efficacy and safety were based on only 10 randomised controlled trials; no real-world observational studies were included.

4.5.6 Conclusion

There is clear and consistent evidence that the recombinant zoster vaccine is effective at reducing herpes zoster cases. The vaccine is effective in those considered at greater risk of herpes zoster aged over 18 years, although efficacy might be slightly lower in these populations than the adult general population aged over 50 years. Although initially effective, the vaccine is associated with waning immunity. While local and systemic adverse events are common with the recombinant zoster vaccine, serious adverse events are uncommon.

5 Rapid review of methodology for economic modelling studies of herpes zoster vaccination

Key points

- The most recent systematic review of economic modelling studies of routine herpes zoster (HZ) vaccination in high-income countries was published in 2019. To establish and assess the most up-to-date international evidence on the approaches taken to the economic modelling of HZ vaccination, a rapid review of studies published since 2018 was undertaken.
- Eighteen additional studies were identified in the rapid review. Combined with the 2019 systematic review, this identifies 45 studies published between 2001 and 2023. With similar characteristics observed among reviews, 23 studies were conducted for European countries, 15 for North America and 7 for the Asia-Pacific region. Eighteen studies were funded by industry; 13 by governments, government agencies and or research bodies; 10 declared no funding, while 4 did not declare details related to funding.
- The method of modelling cost effectiveness has remained consistent across the reviews. Thirty-two of 45 studies employed a Markov model, with a variety of model types employed in the remainder of studies. A shift away from utilising monthly to annual time cycle lengths in Markov models has been noted in more recent studies. Annual cycle lengths were utilised in 83% of Markov models in the updated review compared with 30% of Markov models in the 2019 systematic review.
- Multiple perspectives were adopted in 36% of studies, with similar proportions. A total of 38% of all studies were from the societal perspective only, while 24% were from a payer perspective only.
- Comparing reviews, some differences were noted relating to model structure. More recent studies are more likely to adopt a more comprehensive approach to vaccination age scenarios, incorporate broader health outcomes and incorporate vaccine-related adverse events.
- While overall the appraisal did not raise major concerns with the quality of included studies, there were some concerns with regard to the time horizon adopted, the level of detail provided for parameter data, the

comprehensiveness of the assessment of uncertainty, and the description of model validation.

- Overall methodologies, model structures and model assumptions were generally consistent. However, this rapid review identified several notable modelling features for consideration in the development of a de novo economic model of HZ vaccination for Ireland. These include incorporating monthly Markov cycles to better reflect the natural disease course, including a broader range of health outcomes such as complications other than post-herpetic neuralgia, and incorporating the impact of vaccine-related adverse events.

5.1 Introduction

This chapter reviews the published international evidence on economic evaluations of herpes zoster (HZ) vaccination programmes to inform the economic modelling and assessment of cost effectiveness for Ireland. The review specifically examines the approaches taken to modelling the expected costs and benefits of HZ vaccination targeting the general population.

5.2 Background

A total of 13 different considerations have been identified for modelling and health economic evaluation of vaccines.[251] These considerations include:

- model selection
- time horizon of models
- target population
- natural disease history
- measures of vaccine-induced protection
- duration of vaccine-induced protection
- indirect effects apart from herd protection
- health-related quality of life
- cost components
- perspective adopted
- handling uncertainty
- discounting
- model calibration and validation.

A scoping exercise was undertaken in June 2023 to identify published systematic reviews of economic evaluations of HZ vaccination that detail the economic models employed and the model input parameters. The most recent systematic review

identified that critically assesses cost-effectiveness models for HZ vaccination in an immunocompetent population, with both the herpes zoster live vaccine (ZVL) and recombinant zoster vaccine (RZV), was published in 2019.[252] The review comprised searches in PubMed/MEDLINE, EMBASE and Scopus databases up until March 2018 and included 27 studies, all from high-income countries. The included studies evaluated the cost effectiveness of HZ vaccination, providing relevant data on the type of model employed, model structure, model input parameters, vaccination strategy, vaccine characteristics and economic results. Studies conducted in high-income countries are most likely to be applicable to the Irish setting in terms of model structure and parameter values used.

To establish the most up-to-date evidence of the models employed and parameters used for the economic evaluation of HZ vaccination, and to inform the development of a de novo economic model for Ireland, a rapid review was conducted. The rapid review sought to identify economic evaluations of HZ vaccination that have been published in the five-year period from 2018 (to cover the last search date from the most recent systematic review)[252] to June 2023. The results from the rapid review have been combined with those from the most recent systematic review to provide a comprehensive summary and evaluation of the evidence regarding the approaches taken to modelling the expected costs and benefits of HZ vaccination.

5.3 Rapid review methods

5.3.1 Research question

Research question: What approaches have been used to model the expected costs and benefits of population-level HZ vaccination programmes?

The following Population, Interest, Context (PICo) framework was developed to address the above research question (Table 5.1).

5.3.2 Eligibility criteria

Economic-analysis studies of HZ vaccination programmes in high-income countries which describe the approach to modelling, provide detail on the model structure and model input parameters, include both costs and outcomes in the analysis, and which report a ratio of (incremental) costs to (incremental) benefits, were eligible for inclusion. Studies specifically relating to the vaccination of immunocompromised people, targeted adolescents and or adults, or healthcare workers were not eligible for inclusion.

Table 5.1 PICo for rapid review of methodology for economic modelling studies of herpes zoster vaccination

Population	Immunocompetent adults receiving herpes zoster vaccination.
Interest	Approaches to modelling the expected costs and benefits of herpes zoster vaccination, including, but not limited to: ▪ Model structure ○ type of model ○ perspective adopted ○ time horizon ○ age at vaccination ○ dosing schedule ○ vaccine ○ comparator ○ waning immunity ▪ Model input parameters ○ vaccine efficacy or effectiveness ○ vaccination coverage ○ direct and indirect costs ○ direct and indirect effects ○ utility values for cost-utility analysis ▪ Model outputs ○ economic results that include a ratio of (incremental) costs to (incremental) benefits.
Context	Herpes zoster vaccination programmes in high-income countries.‡

‡As defined by the OECD: WDI - The World by Income and Region (worldbank.org)

5.3.3 Search strategy

A comprehensive electronic search was conducted in CINAHL (EBSCO), Medline (EBSCO) and Embase (Ovid) from 2018 to 26 June 2023, along with a forward citation search of the most recent systematic review.[252] The database search strings (developed in consultation with a librarian), dates of searches and search results are provided in Appendix B: Table A 7 and are publicly available on Zenodo via this link.

5.3.4 Study selection, data extraction and management

Results were exported to Covidence software[253] and screened by one reviewer for relevance. Full-text reviews were assessed for eligibility by one reviewer according to the pre-specified inclusion and exclusion criteria outlined in Table 5.1 and section 5.3.2. Any uncertainty with screening or inclusions was resolved through discussion

with a second reviewer. Data extraction for each study was conducted by one reviewer using a standardised, pre-piloted electronic data extraction form and checked by a second reviewer.

5.3.5 Data extraction and quality appraisal

Table 5.2 details the data that were extracted for each included study. Critical appraisal of all included studies was undertaken using the framework for quality assessment of decision-analytic models proposed by Philips et al.[254] The framework assesses the quality of models under three key domains: structure, data and consistency.

Table 5.2 Data extracted (where available) from each included study

General study characteristics	▪ author name ▪ year of publication ▪ country ▪ type of economic evaluation ▪ population ▪ funding source
Model characteristics	▪ model type ▪ model software ▪ perspective ▪ time horizon ▪ comparator ▪ discount rates for costs and outcomes ▪ sensitivity analysis
Intervention and vaccination strategy	▪ vaccine type (ZVL, RZV, other) ▪ dosing schedule ▪ age at vaccination ▪ coverage rate
Vaccine characteristics	▪ efficacy or effectiveness ▪ waning of immunity
Direct costs **Indirect costs**	▪ type of costs included ▪ methods of measurement and valuation
Direct effects **Indirect effects**	▪ type of effects included ▪ methods of measurement and valuation
Economic results	▪ type of summary ratio ▪ overall healthcare perspective result ▪ overall societal perspective result ▪ authors' conclusions

Key: RZV – recombinant zoster vaccine; ZVL – herpes zoster live vaccine

5.3.6 Data synthesis

Summary characteristics of included studies and the vaccination strategies considered in the models are presented in table format. Findings that were extracted from the included reviews are synthesised narratively. A narrative comparison of findings from the most recent systematic review and the present review is also provided. The reporting of this rapid review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.[178]

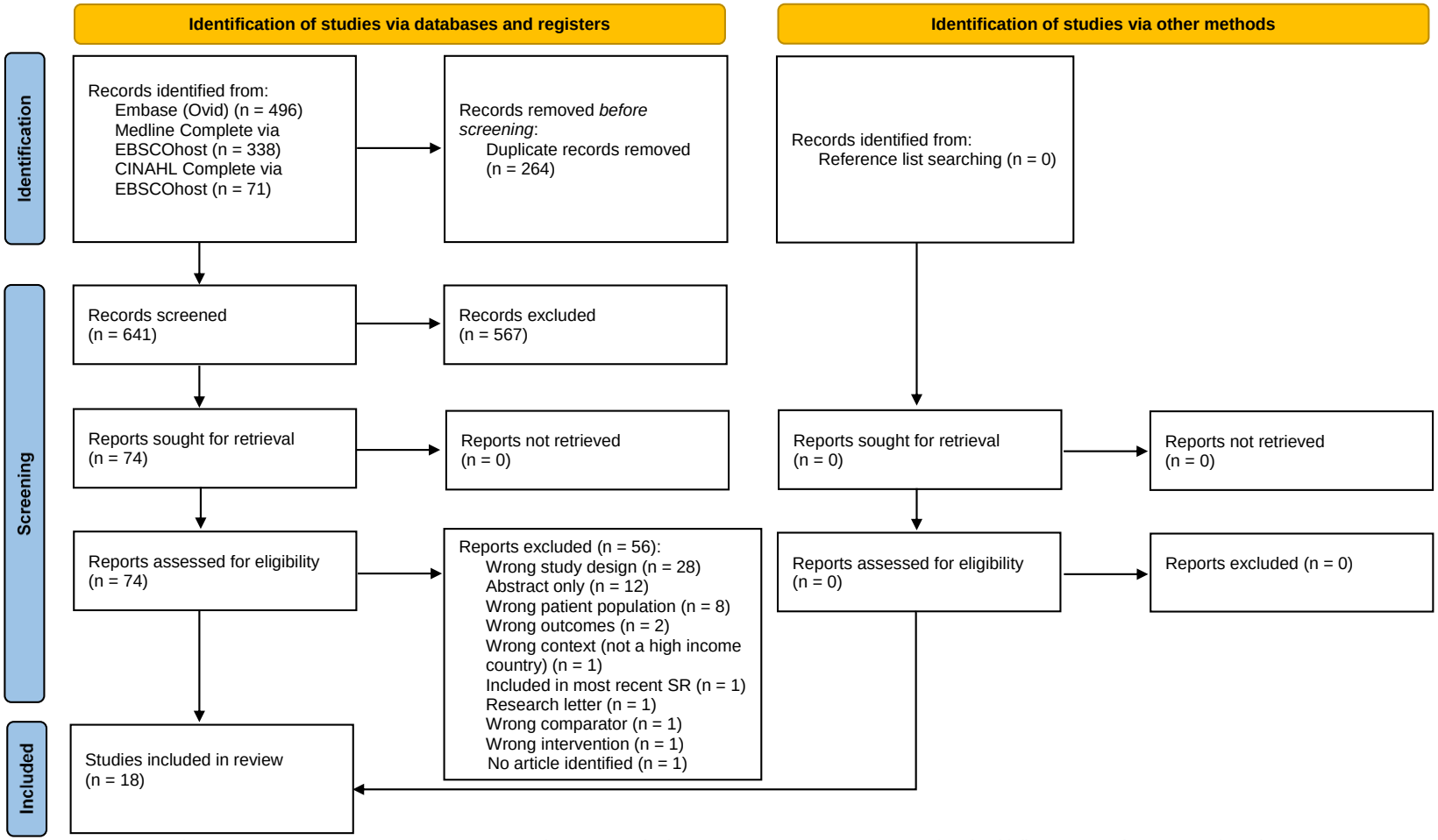
5.4 Results

Following the removal of duplicates, the database searches identified a total of 641 potentially relevant articles. No additional articles were identified in the forward citation search of the most recent systematic review. All articles were screened by title and abstract, and after exclusions, a total of 74 articles remained for full-text review. Following full-text review, 18 studies remained for inclusion in this rapid review (Figure 5.1). A list of studies excluded after full-text review is provided in Appendix B: Table A 8 and full-data extraction tables for included studies are provided in Table A 9.

5.4.1 Characteristics of included studies

A total of 18 model-based studies were identified that met the inclusion criteria for this rapid review. Four studies were published in 2018,[255-258] eight in 2019,[259-266] three in 2021,[246, 267, 268] and three in 2022.[269-271] A total of seven studies were conducted for European countries, two for Germany[246, 265] and one each for Belgium,[270] Italy,[257] the Netherlands,[256] Norway,[269] and Sweden.[268] Of the remaining 11 studies, four were conducted for the United States,[255, 259, 263, 267] three for Japan,[261, 264, 271] and two each for Canada[260, 262] and Hong Kong.[258, 266] An overview of general study characteristics and information on the model structure for included studies is provided in Table 5.1. All studies conducted a cost-utility analysis (CUA), with the exception of one which conducted a cost-benefit analysis (CBA).[267] Eight of the 18 studies were industry-funded: two each from Germany,[246, 265] Japan[264, 271] and the USA,[255, 267] and one each from Canada[262] and Norway.[269] Seven studies were funded by governments, government agencies and or research bodies: two from Hong Kong[258, 266] and one each from Belgium,[270] Canada,[260] Italy,[257] Japan[261] and the USA.[263] Two studies, conducted for the Netherlands[256] and Sweden,[268] declared that they received no funding, while one study, conducted for the USA,[259] did not declare details relating to funding.

Figure 5.1 PRISMA 2020 flow diagram of included studies



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

5.4.2 Model characteristics of included studies

Model

A total of 10 studies employed a Markov model,[246, 255, 258, 259, 262, 264-266, 270, 271] all of which used annual time cycles with the exception of the two studies conducted for Hong Kong that used monthly cycles.[258, 266] Five studies employed decision trees,[256, 257, 261, 263, 267] two of which also had a Markov component,[256, 261] one employed a dynamic transmission model (where both varicella and HZ vaccination were modelled)[268] and two studies employed decision-analytic models, but did not clearly indicate if they were Markov models or decision trees.[260, 269] Of the 10 studies that solely employed a Markov model, six used the same model (ZONA – ZOster ecoNomic Analysis, developed by GSK) which was adapted for individual countries.[246, 255, 262, 264, 265, 271] The number of health states included in the models varied from four to eight. Where four health states were included in the model, they typically comprised the following:

- healthy
- HZ
- post-herpetic neuralgia (PHN) or complications of HZ
- death.

The models with more than four and up to eight health states typically comprised the following states:

- healthy, well, or disease-free
- HZ or uncomplicated HZ
- non-PHN complications of HZ
- PHN
- recovered or resolved HZ
- recurrent HZ
- death from HZ
- death from other causes.

Time horizon

A total of 13 of the 18 included studies adopted a lifetime time horizon, or until the cohort reached at least 100 years old.[246, 255, 258-266, 270, 271] For the remaining five studies, the time horizon specified varied from 15 years[256] to 85 years (where the study assessed both varicella and HZ vaccination) inclusive.[257]

Perspective

Five studies conducted the analysis from the perspective of the payer only, where the 'payer' could represent the tax payer, healthcare payer or healthcare system.[257, 260-262, 270] Six studies conducted the analysis from societal perspective only.[255, 256, 258, 259, 265, 266] Six further studies conducted the analysis from both the payer and societal perspective.[263, 264, 267-269, 271] One study did not clearly specify the perspective adopted, but given that indirect costs were included, it was assumed that the analysis was conducted from the societal perspective.[246]

Discount rates

Costs and benefits arising in the future are usually valued less highly than costs and benefits occurring today. Therefore, discounting of health benefits and health costs reflects society's preferences for benefits to be experienced sooner rather than later and for costs to be experienced in the future rather than the present.[272] The same discount rates were applied for both costs and outcomes in 16 studies, ranging from 1.5% for Canada;[262] 2.0% for Japan;[264, 271] 3.0% for Canada,[260] Germany,[246, 265] Hong Kong,[258, 266] Italy,[257] Japan,[261] Sweden[268] and the US;[259, 263] to 4.0% for Norway. Differential discounting was applied in two studies with discount rates of 3.0% and 1.5% (Belgium)[270] and 4.0% and 1.5% (the Netherlands)[256] used for costs and outcomes, respectively. Of note, when considered at the country level, the two studies for Canada used different discount rates in the base-case scenario[260, 273] while one of the three studies from Japan[261] used a different discount rate compared with the other two studies.[264, 271] In the study funded by government agencies and a health research institute in Canada,[260] a 3.0% discount rate was used and justified by authors, as this is traditionally used when assessing the cost effectiveness of vaccines in Canada. In the second study for Canada,[262] funded by industry, a 1.5% discount rate was used in line with guidelines (4th Edition) from the Canadian Agency for Drugs and Technologies in Health.[274] The two industry funded studies from Japan[264, 271] applied a 2.0% discount rate in line with approved guidelines for the economic evaluation of drugs and medical devices in Japan.[275] In the third government-funded study for Japan, a 3.0% discount rate was used without justification.[261]

Table 5.3 General study characteristics of included studies

Study	Year	Country	Model type and cycle length	Model health states	Time horizon	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
Carpenter et al.[259]	2019	USA	Markov Model (annual time cycles)	1. No HZ 2. HZ 3. Complications of HZ (PHN/HZ ophthalmicus/hospitalisation) 4. Dead	Lifetime	CUA	Societal	3.0%/3.0%	Not stated
Carrico et al.[267]	2021	USA	Decision Tree	'Infected' pathway alternatives included: 1. Complicated (PHN and or non-pain complications) 2. Uncomplicated (end-point) 3. Non-medically attended (end-point) 'Complicated' pathway alternatives included 1. Alive (end-point) 2. Dead (end-point)	30 years	CBA	1. Direct medical 2. Societal	3.0%/3.0%	Industry
Curran et al.[255]	2018	USA	Markov Model (annual time cycles)	1. Healthy 2. HZ 3. PHN (from HZ and recurrent HZ) 4. Non PHN complications (from HZ and recurrent HZ) 5. Recovered 6. Recurrent HZ 7. Death from HZ 8. Death from other causes	Lifetime	CUA	Societal	3.0%/3.0%	Industry
Curran et al.[246]	2021	Germany	Markov Model (annual time cycles)	1. Healthy 2. HZ 3. PHN (from HZ and recurrent HZ) 4. Non PHN complications (from HZ and recurrent HZ) 5. Recovered 6. Recurrent HZ 7. Death from HZ 8. Death from other causes	Lifetime	CUA	Not specified	3.0%/3.0%	Industry
deBoer et al.[256]	2018	the Netherlands	Markov Model with Decision Tree (annual time cycles)	Health states Markov model: 1. Alive/Dead Health states Decision Tree: 1. HZ/No HZ 2. Hospitalisation/No hospitalisation 3. Dead from HZ/Dead from other causes	15 years	CUA	Societal	4.0%/1.5%	None

Study	Year	Country	Model type and cycle length	Model health states	Time horizon	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
Drolet et al. (260)	2019	Canada	Decision-Analytic Model	1. No HZ 2. HZ 3. PHN 4. Dead	Lifetime	CUA	Healthcare system	3.0%/3.0%	Government and Research Body
Flem et al.(269)	2021	Norway	Decision-Analytic Model	1. No HZ 2. HZ 3. PHN 4. Dead	40 years	CUA	1. Healthcare system 2. Societal	4.0%/4.0%	Industry
Hoshi et al.(261)	2019	Japan	Decision Tree and static Markov Model (annual time cycles)	1. Healthy 2. HZ 3. PHN 4. Recovery from HZ/PHN 5. Recurrent HZ 6. Dead	Until cohort reached 100 yrs old	CUA	Payer	3.0%/3.0%	None
McGirr et al.(262)	2019	Canada	Markov Model (annual time cycles)	1. Healthy 2. HZ 3. PHN (from HZ and recurrent HZ) 4. Non PHN complications (from HZ and recurrent HZ) 5. Recovered 6. Recurrent HZ 7. Death from HZ 8. Death from other causes	Lifetime	CUA	Publicly funded healthcare system	1.5%/1.5%	Industry
Melegaro et al.(257)	2018	Italy	Decision Tree	1. Susceptible to HZ 2. Recovered from HZ	25yrs (short), 50yrs (medium) and 85yrs (long-term)	CUA	Taxpayer	3.0%/3.0%	Research Body
Pieters et al.(270)	2022	Belgium	Markov Decision Tree (annual time cycles)	1. Healthy 2. HZ 3. HZ with hospitalisation 4. Death due to HZ	Lifetime of cohort until 103 yrs old	CUA	Healthcare payer	3.0%/1.5%	Government
Prosser et al.(263)	2019	USA	Simulation (state-transition) model (Decision Tree)	1. Disease free 2. Uncomplicated HZ 3. PHN 4. Other complications 5. Post HZ 6. Recurrent HZ 7. Death from HZ 8. Death from other cause	Lifetime	CUA	1. Healthcare sector 2. Societal	3.0%/3.0%	Government
Shiragami et al.(264)	2019	Japan	Multi-cohort Markov Model (annual time cycles)	1. No HZ 2. HZ 3. PHN 4. HZ-related complications (non-	Remaining lifetime of cohort	CUA	1. Payer 2. Societal (scenario analysis)	2.0%/2.0%	Industry

Study	Year	Country	Model type and cycle length	Model health states	Time horizon	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
				PHN) 5. Recurrent HZ 6. HZ-related death 7. Death due to natural causes					
Teng et al.[271]	2022	Japan	Multi-cohort Markov Model (annual time cycles)	1. No HZ 2. HZ 3. PHN 4. HZ-related complications (non-PHN) 5. Recurrent HZ 6. HZ-related death 7. Death due to natural causes	Remaining lifetime of cohort	CUA	1. Payer 2. Societal	2.0%/2.0%	Industry
Van Oorschot et al.[265]	2019	Germany	Multi-cohort Markov Model (annual time cycles)	1. No HZ 2. HZ 3. PHN 4. Recovered 5. Recurrent HZ 6. Death from HZ 7. Death from natural causes	Remaining lifetime of cohort	CUA	Societal	3.0%/3.0%	Industry
Wolff et al.[268]	2021	Sweden	Age-structured Dynamic Markov Transmission Model	1. Susceptible to HZ 2. Vaccinated against HZ 3. Ill with HZ 4. Recovered from HZ	20 yrs	CUA	1. Healthcare Payer 2. Societal	3.0%/3.0%	None
You et al.[258]	2018	Hong Kong	Markov Model (monthly time cycles)	1. Well 2. HZ 3. PHN 4. HZ-related complications (non-PHN) 5. Resolved HZ 6. HZ related death 7. Death due to natural causes	Lifelong	CUA	Societal	3.0%/3.0%	Government
You et al.[266]	2019	Hong Kong	Markov Model (monthly time cycles)	1. Healthy 2. HZ 3. HZ-related complication 4. PHN 5. Recovered HZ 6. Recurrent HZ 7. HZ-related death 8. Death due to natural causes	Until cohort reached 100 yrs old	CUA	Societal	3.0%/3.0%	Government

Key: CBA – cost-benefit analysis; CUA – cost-utility analysis; HZ – herpes zoster; PHN – post-herpetic neuralgia

5.4.3 Intervention and vaccination strategies

Three of the 18 studies assessed herpes zoster live vaccine (ZVL) vaccination strategies only,[257, 268, 269] eight assessed recombinant zoster vaccine (RZV) strategies only,[246, 255, 258, 262, 264-266, 271] five assessed both RZV and ZVL strategies[256, 259, 260, 263, 270] and one assessed both RZV and a live varicella vaccine (VVL).[261] The remaining study (a CBA of HZ vaccination in the USA) assumed that ZVL was used exclusively for the first year of the study and that RZV was exclusively used for subsequent years.[267]

All studies, with the exception of three,[256, 261, 270] assessed one-dose ZVL and or two-dose RZV. The studies conducted for the Netherlands and Belgium assessed one-dose ZVL, two-dose RZV and one-dose ZVL plus a booster dose after 10 years,[256, 270] while one of the studies conducted for Japan assessed both one- and two-dose RZV and one-dose VVL.[261] Additionally, the study for Japan considered vaccination of females and males separately.[261]

The age at vaccination in included studies ranged from 50 years to 99 years old inclusive, with the majority of studies assessing multiple strategies with varying ages at vaccination. Of the 18 included studies, 12 assessed specific fixed ages at vaccination ranging from 50 years [246, 256, 258-260, 266, 267, 270] to 85 years old,[260, 270] with one study assessing vaccination at each year (of 31 years) from 50 years to 80 years old inclusive for males and females separately.[266] Two studies assessed vaccination strategies with specific age ranges for eligibility; a US study assessed multiple strategies with 10-year age ranges from 50 to 99 years inclusive,[263] and a Japanese study assessed multiple strategies varying from a 20-year age range from 65 to 84 years old inclusive, to a five-year age range from 80 to 84 years old inclusive.[261] Seven studies assessed vaccination strategies with broader age-based eligibility; these strategies included vaccination at 50 years and older, 60 years and older, 65 years and older, and or 70 years and older.[246, 255, 262, 264, 271] Two studies included strategies with catch-up programmes.[257, 269] The study for Norway assessed three specific strategies with and without catch-up in the first year of the vaccination programme; vaccination at 60 years old (with catch-up in 60- to 70-year-olds), vaccination at 65 years old (with catch-up in 65- to 70-year-olds), and vaccination at 70 years old (with catch-up in 70- to 80-year-olds).[269] The study for Italy assessed a strategy with vaccination at age 65 years and older, either alone or in combination with an initial catch-up programme in those aged 66 to 75 years inclusive.[257] Vaccination coverage rates varied considerably in included studies. Seven of the 18 studies reported that coverage rates were based on those for other adult vaccination programmes in that country (e.g., influenza, pneumococcal, hepatitis).[255, 261, 262, 264, 268, 270, 271] First-dose coverage with RZV and ZVL ranged

from 24% to 100%, with second-dose coverage for RZV ranging from 69% to 100%.

5.4.4 Vaccine characteristics

The majority of studies (n=14) reported that vaccine-efficacy rates were obtained from published randomised controlled trials (RCTs) including the Shingles Prevention Study (SPS) and the Zoster Efficacy and Safety Study (ZEST) for ZVL,[276, 277] and the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50), Zoster Efficacy Study in Adults 70 Years of Age or Older (ZOE-70) and ZOE long-term follow-up (LTFU) study for RZV.[194, 195, 197] Of the remaining four studies, three did not specifically state the data sources and included references only,[257, 267, 268] while the fourth study for Norway sourced the data from two cohort studies conducted in the USA.[269]

Of the nine studies that assessed ZVL vaccination strategies, five reported using age-specific vaccine efficacy rates against herpes zoster only,[256, 259, 263, 267, 270] while one reported using separate age-specific vaccine efficacy rates against HZ and PHN.[269] Two further studies used single efficacy rates for the entire study cohort; one used a single efficacy rate against HZ,[257] and the second study used separate efficacy rates against HZ and PHN.[268] The final study did not clearly report the vaccine efficacy rates used in the analysis.[260] Age-specific ZVL efficacy rates against HZ used in the analysis generally ranged from 63.9% for those vaccinated at age 50 to 69 years to 30% for those vaccinated at age 70 years and over. ZVL efficacy rates against PHN generally ranged from 85% for those vaccinated at age 50 to 69 years to 77% for those vaccinated at age 80 years and older. The efficacy rates applied in all included studies are reported in full in Table 5.4.

Of the 15 studies that assessed RZV vaccination strategies, nine provided vaccine efficacy rates for both one- and two-dose RZV; seven of these studies provided age-specific efficacy rates,[255, 261-265, 271] while two studies provided a single efficacy rate for the entire study cohort.[258, 266] Of the remaining six studies that assessed RZV vaccination, one provided age-specific vaccine efficacy rates for two-dose RZV only,[246] four provided age-specific efficacy rates for RZV without specifying dosage[256, 259, 267, 270] and the final study did not clearly report the rates used in the analysis.[260] Age-specific RZV efficacy rates reported ranged from 95.8% to 98.9% for those aged 50 to 69 years at vaccination and from 95.4% to 99.2% for those aged 70 years and older. Where age-specific RZV efficacy rates by dose were clearly reported, they were generally consistent; 90% and 98% efficacy for one and two doses, respectively, for those aged 50 to 69 years at vaccination, and for those aged 70 years and older at vaccination, an efficacy rate of 69% for one dose and ranging from 95.4% to 97.8% for two doses.

Only one of the 18 studies included in this review did not incorporate waning immunity,[257] while four further studies did not provide specific data relating to waning immunity.[260, 268-270] Annual waning rates and duration of protection varied considerably among the 13 studies that reported data. Two studies applied linear annual waning rates for ZVL ranging from 5.4%[259] to 8.07% per annum.[256] Two studies reported duration of protection with ZVL; one applied 12 years protection for those vaccinated at age 50 to 69 years and six years protection for those vaccinated at age 70 years and older.[267] The second study assumed 12 years of protection for those vaccinated at age 50 years, 10 years for those vaccinated at age 60 years, seven years for those vaccinated at age 70 years, four years for those vaccinated at age 80 years and one year for those vaccinated at age 90 years.[263]

Linear annual waning rates were applied to RZV in three studies; waning rates ranged from 5.07% to 8% per annum for one-dose RZV.[258, 259, 266] For two-dose RZV, waning rates ranged from 3.19% per annum from year three after vaccination to 5.44% per annum.[258, 259, 266] Two studies reported using age-specific waning rates for RZV.[246, 256] In a study for Germany, annual waning rates for two-dose RZV ranged from 1.5% per annum for those vaccinated at age 50 to 69 years to 2.3% per annum for those vaccinated at age 70 years and older.[246] In the study for the Netherlands, an annual waning rate of 0.9% was applied to those vaccinated at age 50 to 69 years in years one to four after vaccination and 4.1% thereafter.[256] In the same study, an annual waning rate of 4.1% per annum was applied to those vaccinated at age 70 years and older.[256] Six studies applied waning rates for one-dose RZV based on years since vaccination and or applied waning rates for two-dose RZV based on both years since vaccination and age of the vaccine recipient (Table 5.4).[255, 261, 262, 264, 265, 271] Two further studies reported duration of protection with RZV, one of which reported by dose. The first study applied 30 years duration of protection for those vaccinated at age 50 to 69 years and 22 years for those vaccinated at age 70 years and older.[267] The second study applied 11 years (one-dose) and 19.4 years (two-dose) duration of protection for those vaccinated at age 50 to 69 years and four years (one-dose) and 18.8 years (two-dose) for those vaccinated at age 70 years and older.[263]

Table 5.4 provides a summary of the herpes zoster vaccination strategies considered in the models and associated vaccine characteristics.

Table 5.4 Vaccination strategies and vaccine characteristics considered in models evaluating herpes zoster vaccination

Study	Year	Vaccine	Vaccine dosage schedule	Age at vaccination	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
Carpenter et al.[259]	2019	ZVL and RZV	ZVL: 1-dose RZV: 2-dose	50 yrs, 60 yrs, 70 yrs	ZVL 50-59 yrs: 69.8%; 60-69 yrs: 65.7%; 70-79 yrs: 40.7%; 80-100 yrs: 15.7% RZV 50-59 yrs: 96.9%; 60-69 yrs: 94.1%; 70-79 yrs: 89.9%; ≥80 yrs: 89.7%	ZVL 5.44% p.a. RZV (assumed) 1-dose: 8% p.a. 2-dose: 5.44% p.a.	First dose not stated (but assumed 100%) and assumption that 95.5% returned for second dose of RZV
Carrico et al.[267]	2021	ZVL and RZV (ZVL used exclusively in 2017, followed by exclusive use of RZV from 2018)	ZVL: 1-dose RZV: 2-dose	50 yrs	ZVL 50-69 yrs: 63.9%; ≥70 yrs: 30.0% RZV 50-69 yrs: 95.8%; ≥70 yrs: 89.1%	ZVL (duration of protection) 50-69 yrs: 12 yrs; ≥70 yrs: 6 yrs RZV (duration of protection) 50-69 yrs: 30 yrs; ≥70 yrs: 22 yrs	First dose: 50-59 yrs: 0.0%*; 60-64 yrs: 23.9%; ≥65 yrs: 37.4% Second dose: 69.0% *Assumed that HZ vaccine coverage for ages 50-59 yrs reaches current coverage level of 60-64 yr-old age group (23.9%) five years after introduction of RZV in year 2 (2018).
Curran et al. [255]	2018	RZV	RZV: 2-dose	≥60 yrs	RZV 1-dose 50-69 yrs: 90.1%; ≥70 yrs: 69.5% RZV 2-dose 50-69 yrs: 98.4%; ≥70 yrs: 97.8%	RZV 1-dose (assumed same as ZVL) Years 1-4: 5.4% p.a.; Year 5 onwards: 5.1% p.a. RZV 2-dose Years 1-4: 1% p.a.; Year 5 until 69 yrs old: 2.35% p.a.; ≥70 yrs: 3.6% p.a. (bootstrap analysis)	First dose: 100% Second dose: 69.0%
Curran et al. [246]	2021	RZV	RZV: 2-dose	50 yrs, 60 yrs, 65 yrs, 70 yrs, ≥50 years, ≥60 years, ≥70 years	RZV 2-dose 50-69 yrs: 98.9%; ≥70 yrs: 95.4%	RZV 2-dose 50-69 yrs: 1.5% p.a.; ≥70 yrs: 2.3% p.a.	First dose: 40% Second dose: 70%
deBoer et al. [256]	2018	ZVL and RZV	ZVL: 1-dose ZVL: 1-dose + booster (after 10 yrs) RZV: 2-dose	50 yrs, 60 yrs, 70 yrs, 80 yrs	ZVL Specific values not provided. RZV 50-69 yrs: 98.1%; ≥70 yrs: 99.2%	ZVL 8.07% p.a. RZV 50-69 yrs: 0.9% p.a. for Years 1-4 and 4.1% p.a. thereafter; ≥70 yrs: 4.1% p.a.	First dose: 50% Second dose: 100%

Study	Year	Vaccine	Vaccine dosage schedule	Age at vaccination	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
Drolet et al. [260]	2019	ZVL and RZV	ZVL: 1-dose RZV: 2-dose	50 yrs, 60 yrs, 65 yrs, 70 yrs, 75 yrs, 80 yrs, 85 yrs	Not provided	Not provided	Not provided
Flem et al.[269]	2021	ZVL	ZVL: 1-dose	60 yrs (without and with catch-up in 60-70 yr-olds in year 1 of programme), 65 yrs (without and with catch-up in 65-70 yr-olds in year 1 of programme), 70 yrs (without and with catch-up in 70-80 yr-olds in year 1 of programme)	Provided in a graph. <u>ZVL against HZ</u> 60-69 yr-olds: 70% at vaccination; 40% at 5 yrs post-vaccination; 28% at 10 yrs post-vaccination; 15% at 15 yrs post-vaccination; 4% at 20 yrs post-vaccination 70-79 yr-olds: 65% at vaccination; 33% at 5 yrs post-vaccination; 12% at 10 yrs post-vaccination; 0% at 15 yrs post-vaccination ≥80 yr-olds: 65% at vaccination; 27% at 5 yrs post-vaccination; 8% at 10 yrs post-vaccination; 0% at 15 yrs post-vaccination <u>ZVL against PHN</u> 60-69 yr-olds: 85% at vaccination; 60% at 5 yrs post-vaccination; 45% at 10 yrs post-vaccination; 28% at 15 yrs post-vaccination; 13% at 20 yrs post-vaccination; 0% at 25 yrs post-vaccination 70-79 yr-olds: 85% at vaccination; 55% at 5 yrs post-vaccination; 36% at 10 yrs post-vaccination; 18% at 15 yrs post-vaccination; 0% at 20 yrs post-vaccination ≥80 yr-olds: 77% at vaccination; 56% at 5 yrs post-vaccination; 39% at 10 yrs post-vaccination; 22% at 15 yrs post-vaccination;	Data not specifically provided	Main cohort (non-catch-up): 30% in Yr1, 40% in Yr2, 50% in Yrs3+ Catch-up: 30% during first year of the programme only

Study	Year	Vaccine	Vaccine dosage schedule	Age at vaccination	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
					4% at 20 yrs post-vaccination; 0% at 25 yrs post-vaccination		
Hoshi et al.[261]	2019	RZV (and VVL)	RZV: 1-dose RZV: 2-dose VVL: 1-dose	65-84 yrs, 70-84 yrs, 75-84 yrs, 80-84 yrs	RZV 1-dose 65-69 yrs: 90%; ≥70 yrs: 69.0% RZV 2-dose 65-69 yrs: 100%; ≥70 yrs: 97.0% VVL (Year 1) 65-69 yrs: 70.6%; 70-79 yrs: 64.5%; ≥80 yrs: 63.7%	RZV 1-dose 65-69 yrs: 9.1% p.a.; ≥70 yrs: 25% p.a. RZV 2-dose 65-69 yrs: 5.15% p.a.; ≥70 yrs: 5.32% p.a. VVL 65-69 yrs: non-linear and no protection from Year 9 70-79yrs: non-linear and no protection from Year 8 ≥80 yrs: non-linear and no protection from Year 7	First dose: 40.8% Second dose: 80%
McGirr et al.[262]	2019	RZV	RZV: 2-dose	≥60 yrs (and ≥50 yrs in supplementary analysis)	RZV 1-dose HZ and PHN: 50-59 yrs: 90.0%; 60-64 yrs: 90.0%; 65-69 yrs: 90.0%; 70-79 yrs: 69.5%; ≥80 yrs: 69.5% RZV 2-dose HZ and PHN: 50-59 yrs: 98.4%; 60-64 yrs: 98.4%; 65-69 yrs: 98.4%; 70-79 yrs: 97.84%; ≥80 yrs: 97.84%	RZV 2-dose 50-59 yrs, 60-64 yrs and 65-69 yrs: 1.0% p.a. for first four years and 2.3% p.a. thereafter 70-79 yrs and ≥80 yrs: 3.6% p.a. constant	RZV First dose: 80%; Second dose: 75%
Melegaro et al.[257]	2018	ZVL	ZVL: 1-dose	≥65 yrs either alone or in combination with an initial catch-up campaign (66-75 yrs)	ZVL 50%	Not incorporated	60%
Pieters et al.[270]	2022	ZVL and RZV	ZVL: 1-dose ZVL: 1-dose + booster (after 10 yrs)	50 yrs, 60 yrs, 70 yrs, 80 yrs, 85 yrs	Values used not clear as data not provided. ZVL Efficacy at vaccination (read	Data not provided	First dose (all vaccines): 46.2% Second dose/booster: 100%

Study	Year	Vaccine	Vaccine dosage schedule	Age at vaccination	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
			RZV: 2-dose		from graph) 50 yr-olds: 66%; 60 yr-olds: 66%; 70 yr-olds: 50%; 80 yr-olds: 25%; 85 yr-olds: 15% RZV (from RCT data) ≥50 yrs: 98.4% ≥70 yrs: 97.6%		
Prosser et al.[263]	2019	ZVL and RZV	ZVL: 1-dose RZV: 2-dose	50-59 yrs, 60-69 yrs, 70-79 yrs, 80-89 yrs, 90-99 yrs	ZVL 50 yr-olds: 78.1%; 60 yr-olds: 77.9; 70 yr-olds: 65.9%; 80 yr-olds: 38.5%; 90 yr-olds: 9.5% RZV 1-dose 50-69 yrs: 90%; ≥70 yrs: 69% RZV 2-dose 50-69 yrs: 100%; ≥70 yrs: 97.0%	ZVL (waning duration) 50 yr-olds: 12 yrs; 60 yr-olds: 10 yrs; 70 yr-olds: 7 yrs; 80 yr-olds: 4 yrs; 90 yr-olds: 1 yr RZV 1-dose (waning duration) 50-69 yrs: 11 yrs ≥70 yrs: 4 yrs RZV 2-dose (waning duration) 50-69 yrs: 19.4 yrs ≥70 yrs: 18.8 yrs	ZVL: not reported RZV 2-dose: 100%
Shiragami et al.[264]	2019	RZV	RZV: 2-dose	≥65 yrs base case (plus ≥50 yrs, ≥60yrs, ≥70 yrs)	RZV 1-dose 50-69 yrs: 90.0%; ≥70 yrs: 69.5% RZV 2-dose 50-69 yrs: 98.4%; ≥70 yrs: 97.84%	RZV 1-dose Years 1-4: 5.4% p.a. Years 5+: 5.1% p.a. RZV 2-dose <70yrs: 1.0% p.a. in years 1-4; 2.3% p.a. year 5+ ≥70 yrs: 3.6% p.a.	First dose: 40% Second dose: 95%
Teng et al.[271]	2022	RZV	RZV: 2-dose	65 yrs base case (plus ≥50 yrs, ≥65 yrs, 50 yrs, 60 yrs, 70 yrs, 80 yrs)	RZV 1-dose 50-69 yrs: 90.0%; ≥70 yrs: 69.5% RZV 2-dose 50-69 yrs: 98.9%; ≥70 yrs: 95.4%	RZV 1-dose Years 1-4: 5.4% p.a. Years 5+: 5.1% p.a. RZV 2-dose 50-69 yrs: 1.5% p.a. ≥70 yrs: 2.3% p.a.	First dose: 40% Second dose: 95%
Van Oorschot et al.[265]	2019	RZV	RZV: 2-dose	60 yrs, 65 yrs, 70 yrs, 80 yrs	RZV 1-dose efficacy against HZ and PHN 60-69 yrs: 90.0%;	RZV 1-dose Years 1-4: 5.4% p.a. Years 5+: 5.1% p.a.	First dose: 40% Second dose: 70%

Study	Year	Vaccine	Vaccine dosage schedule	Age at vaccination	Vaccine efficacy/ effectiveness	Waning	Vaccination coverage
					≥70 yrs: 69.5% RZV 2-dose efficacy against HZ 60-69 yrs: 98.4%; ≥70 yrs: 97.8%	RZV 2-dose <70 yrs: 1.0% p.a. in years 1-4; 2.3% p.a. year 5+ ≥70 yrs: 3.6% p.a.	
Wolff et al.[268]	2021	ZVL	ZVL: 1-dose	65 yrs	ZVL 64% against HZ; 73% against PHN	Average duration of 4 yrs but yearly data not provided	50%
You et al.[258]	2018	RZV	RZV: 2-dose	50 yrs, 60 yrs, 70 yrs	RZV 1-dose 88.01% RZV 2-dose Years 1-2: 100%	RZV 1-dose 5.07% p.a. RZV 2-dose Year 3 onwards: 3.19% p.a.	First dose: 100% Second dose: 100% (males and females)
You et al.[266]	2019	RZV	RZV: 2-dose	Yearly ages from 50 yrs to 80 yrs inclusive for males and females separately	RZV 1-dose 88.01% RZV 2-dose Years 1-2: 100%	RZV 1-dose 5.07% p.a. RZV 2-dose Year 3 onwards: 3.19% p.a.	First dose: 100% Second dose: 100% (males and females)

Key: HZ – herpes zoster; PHN – post-herpetic neuralgia; RZV – recombinant zoster vaccine; VVL – live varicella vaccine; ZVL – herpes zoster live vaccine

5.4.5 Costs

Direct costs

Across all studies, direct costs detailed in the economic modelling generally included some or all of the following:

- Direct medical costs
    - GP visits
    - outpatient clinic visits
    - hospitalisation, including hospitalisation for stroke as a result of HZ
    - prescription and over-the-counter medication
    - laboratory tests
    - therapeutic appliances.
- Patient costs
    - prescription and over-the-counter medication
    - travel for a GP visit, hospitalisation, specialist care, and or to acquire medication and vaccination.
- Vaccination costs
    - vaccine procurement
    - vaccine administration
    - vaccine-related adverse event
    - vaccine-related adverse event requiring medically attended visit (e.g., GP visit, outpatient visit, emergency room visit, hospitalisation).

A total of 12 studies specifically included the cost of vaccine-related adverse events.[246, 255, 258, 259, 262-267, 269, 271]

Indirect costs

Where studies conducted the analysis from the societal perspective, indirect costs detailed in the economic modelling included productivity losses associated with some or all of the following:

- work absenteeism and presenteeism for patients with HZ and associated complications (by disease severity, complication and or pain level)
- work absenteeism for caregivers of those with HZ
- HZ-related mortality
- patient time required for vaccination

- patient time required for care for a vaccine-related adverse event (e.g., visit to a pharmacy physician's office or emergency department).

Additionally, unrelated healthcare costs in gained life years (per averted herpes zoster-related death) were included in one study.[256] Three studies specified that they adopted the friction-cost approach when estimating productivity losses.[256, 258, 266] In the study for the Netherlands, a friction period of 84 days was applied for HZ-related deaths.[256] For both studies conducted for Hong Kong, the friction period was assumed to be the duration of medical leave.[258, 266] A single study reported using the human capital approach to estimate productivity losses.[267] Data required to measure and value costs, where reported, are included in the data extraction tables in Appendix B: Table A 9.

5.4.6 Effects

Direct effects

Across all studies, the direct effect of HZ vaccination on either the incidence or burden associated with HZ included in the economic modelling generally incorporated some or all of the following, with outcomes stratified in some studies by gender and age:

- HZ (by pain severity)
- PHN (by pain severity)
- recurrent HZ (one-time or repeated)
- recurrent herpes zoster with PHN
- non-PHN complications
    - ocular
    - neurological
    - cutaneous
    - cosmetic
    - other non-pain complications.
- outpatient cases of HZ
- hospitalised cases of HZ
- HZ-related death.

A total of 10 studies (56%) considered non-PHN complications (e.g., ocular, neurological, cutaneous and cosmetic) separately in the model.[255, 258-260, 262-264, 266, 268, 271]

Vaccine-related adverse events

A total of 12 studies (67%) reported that adverse events related to vaccination were incorporated into the model and included the following:[255, 258, 259, 261-264, 266-269, 271]

- local/injection site reaction (by vaccine)
- systemic reaction/general adverse event
- serious adverse event
- vaccine-related reaction leading to GP visit
- vaccine-related reaction leading to outpatient visit
- vaccine-related reaction leading to emergency room visit
- vaccine-related reaction leading to hospitalisation.

Where reported, data required to measure and value effects are included in the data extraction tables in Appendix B: Table A 9.

Utility weights for quality-adjusted life-years (QALYs)

Baseline utility weights were reported in 11 of 18 included studies; six studies reported them by age group,[246, 255, 262, 264, 265, 271], a further four reported them by sex and age group[258, 263, 266, 269] and one study reported a baseline utility weight for the overall study cohort (adults aged 50 years and older).[256]

Utility weights or utility decrements per health effect, used to calculate QALYs, were clearly reported in six of the 17 reviews that conducted a CUA,[256, 258, 261, 266, 269, 270] with two of these studies also reporting associated calculated QALY losses.[256, 269] Four of the six studies specifically reported that the utility values used to calculate QALYs were derived using the Euro-QoL five-dimension scale (EQ-5D) instrument.[256, 258, 261, 266] Ten further studies solely reported QALY losses associated with the disease states,[246, 255, 257, 259, 260, 262, 264, 265, 268, 271] two of which specifically reported that the utility values used to calculate QALYs were derived using the Euro-QoL five-dimension scale (EQ-5D) instrument.[262, 265] One study reported quality-of-life adjustments for various disease states, but the data were unclear.[263]

Two studies reported utility weights for HZ by pain severity (mild, moderate and severe),[256, 270] while one study reported utility decrements, also by pain severity, for herpes zoster and PHN separately.[269] Two further studies reported HZ utility decrements for outpatients, and inpatients both with and without complications and a utility decrement for PHN.[258, 266] One study reported utility weights separately for HZ and PHN by age group (65- to 69-year-olds, 70- to 79-year-olds, 80 years and older).[261] A single study reported quality-of-life adjustments by age group for ocular complications, but the data were unclear.[263] Two studies reported the utility

decrement associated with injection site reaction and serious adverse events following vaccination.[258, 266]

Of the 10 studies that only reported QALY losses, eight reported separate losses for herpes zoster and PHN. One study reported by pain severity (none, mild, moderate, severe),[259] and eight reported by various age groups,[246, 255, 257, 260, 264, 265, 268, 271] one of which reported QALY losses for vaccinated and unvaccinated individuals separately.[255] A single study reported using an overall QALY loss for HZ.[262]

Overall, the reporting of utility weights and duration of time spent in health states used to calculate QALY losses varied greatly. Average QALY losses associated with HZ by pain severity generally ranged from 0.020 for no pain to 0.058 for severe pain.[259] Where QALY losses for HZ were reported by age group, they generally ranged from 0.005[255] to 0.014[264, 271] for those in the 50- to 59-year-old age group, to 0.012 in the 70 years and older age group[255] and 0.201 in the 85 years and older age group.[268] Where QALY losses specifically associated with PHN were reported, they ranged from 0.310 for no pain to 0.770 for severe pain.[259] Where average QALY losses for PHN were reported by age group, they generally ranged from 0.041[260] to 0.118[264, 271] for those in the 50- to 59-year-old age group and up to 0.286 in the 70- to 74-year-old age group.[269] The two studies that did not report QALY losses for HZ and PHN separately reported considerably higher average QALY losses for HZ compared with those studies that reported the QALY losses separately; QALY losses associated with HZ in the two studies ranged from 0.022 in those up to 34 years of age, to 0.201 in those aged 85 years and older.[257, 268] A QALY loss of 0.240 for ocular complications was reported in one study.[259] The QALY loss associated with adverse events of vaccination was reported in seven studies and generally ranged from 0.0001 for common adverse events to 0.0082 for serious adverse events.[255, 259, 260, 262, 264, 269, 271]

5.5 Economic results

All but one of the 18 included studies calculated incremental cost-effectiveness ratios (ICERs), reporting incremental costs per quality-adjusted life year (QALY) gained or saved. A single study conducting a cost-benefit analysis, reported a benefit-cost ratio.[267]

Three studies, conducted for Italy, Norway and Sweden, assessed the cost effectiveness of ZVL vaccination, versus no vaccination, with the following results:

- From the tax payer perspective in Italy, ICERs for a strategy of vaccinating adults aged 65 years and older with ZVL, versus no vaccination, with and without catch-up for 66- to 74-year-olds, demonstrated cost effectiveness.[257]

- From both the health care system and societal perspectives in Norway, ICERs for ZVL vaccination with catch-up, compared with no vaccination, were lower than ICERs without catch-up. ICERs were lowest for the age group vaccinated at 65 years.[269]
- From the healthcare payer and societal perspectives in Sweden, ICERs for herpes zoster vaccination with ZVL, versus no vaccination, exceeded €250,000/QALY gained and was deemed not cost effective when a WTP threshold of €50,000 per QALY gained was assumed.[268]

Nine studies, conducted for Canada (n=1), Germany (n=2), Hong Kong (n=2), Japan (n=3) and the USA (n=1), assessed the cost effectiveness of RZV vaccination strategies, versus no vaccination and or vaccination with ZVL or VVL, with the following results:

- In a study conducted from the healthcare system perspective for Canada, vaccination with RZV in adults aged 60 years and over was deemed cost effective versus both no vaccination and vaccination with ZVL.[262]
- From the societal perspective, RZV vaccination was cost effective compared with no vaccination for Germany at a hypothetical WTP threshold of €50,000 per QALY gained; ICERs for RZV vaccination in those 60 years and older were less than those 70 years and older, versus no vaccination.[265] A second study for Germany also reported lower ICERs for vaccination at 60 years old than 70 years old, versus no vaccination.[246]
- A study conducted from the societal perspective for Hong Kong reported that the ICERs for RZV vaccination, versus no vaccination, were lowest in the 70-year-old age group.[258] A second follow-up study for Hong Kong that assessed strategies for males and females separately, found that ICERs for RZV vaccination, versus no vaccination, were lowest in the 60- and 70-year-old age groups.[266]
- One study conducted from the payer perspective for Japan reported that vaccinating individuals in the 65- to 84-year-old age group with RZV may be cost effective, versus the next best alternative vaccination strategy (VVL in 70 to 84 year-olds).[261] A second study for Japan, conducted from both the payer and societal perspectives, reported that ICERs for RZV vaccination, compared with no vaccination, were lowest in the 65 years and older age group.[264] A more recent study (with an updated vaccine price) also found that that ICERs for RZV vaccination, compared with no vaccination, were lowest in the 65-year-old age group.[271]
- In the study conducted from the societal perspective in the US, RZV vaccination in those aged 60 years was cost effective compared with no

vaccination, and the strategy was cost saving compared to ZVL vaccination.[255]

Five studies, conducted for Belgium (n=1), Canada (n=1), the Netherlands (n=1) and the USA (n=2), assessed the cost effectiveness of both ZVL and RZV with the following results:

- From the healthcare payer perspective in Belgium, RZV vaccination in various age groups from 50- to 85-year-olds was not cost effective, versus no vaccination, at a WTP threshold of €40,000 per QALY gained.[270] However, results were highly sensitive to duration of protection and the price of the vaccine. ZVL vaccination was either not cost effective compared with no vaccination or was dominated by RZV vaccination (differed by age group).[270]
- From the Canadian healthcare system perspective, lower ICERs were reported for ZVL vaccination than for RZV vaccination when each of these options were compared with no vaccination at various ages from 50 years old. RZV vaccination was likely cost effective in Canada for adults aged 60 years and older, and likely more cost effective than ZVL vaccination.[260]
- From the societal perspective, all vaccination strategies (at various ages) with RZV or ZVL for the Netherlands dominated (that is, was more effective and less costly than) no vaccination.[256]
- From the societal perspective in the USA, lower ICERs were reported for RZV vaccination than for ZVL vaccination when each of these options were compared with no vaccination across age groups. When the two vaccines were directly compared, RZV vaccination dominated ZVL.[259] In a second study conducted from both the healthcare sector and societal perspectives for the USA, ICERs for RZV vaccination, compared with no vaccination, across age groups ranging from 50- to 59-year-olds to 90- to 99-year-olds, were all lower than USD 61,000 per QALY gained, with the lowest ICERs reported in the 80- to 89-year-old age group.[263] In the same study, the estimated ICERs RZV vaccination, compared with no vaccination, were lower than those for ZVL vaccination compared with no vaccination. When RZV and ZVL vaccination strategies were directly compared, RZV vaccination dominated (that is, was more effective and less costly).[263]

In the single study that conducted a cost-benefit analysis, the benefit-cost ratio for vaccination (ZVL until 2017 and RZV thereafter), compared with no vaccination, was less than one from the direct medical perspective and greater than one from the societal perspective.[267]

5.6 Conclusions from studies

Of the three studies that assessed ZVL vaccination only, two concluded that vaccination was cost effective, versus no vaccination, from the payer or tax payer perspective. The study for Italy concluded that the newly introduced HZ vaccination strategy (at 65 years of age and older) in Italy was expected to be cost effective and that an additional catch-up campaign for HZ vaccination targeting people aged 66 to 75 years would further increase the programme benefits.[257] The study from Norway concluded that vaccinating adults at 65 years of age with catch-up up to 70 years in the first year of the programme was the most cost-effective strategy.[269]

Of the nine studies that assessed RZV only, those conducted from the societal perspective for both the USA[255] and Germany[246, 265] concluded that vaccination with RZV from 60 years and older was cost effective versus no vaccination. In the case of Germany, it was concluded that, compared with no vaccination, starting vaccination against HZ with RZV in the population aged 60 years and older would also be more cost effective than starting vaccination at age 70 years and older. Similarly, a study conducted from the healthcare system perspective for Canada concluded that RZV would be cost effective in the Canadian population aged 60 years and older, compared with both no vaccination and vaccination with ZVL.[262] Two studies from Hong Kong had differing conclusions. One study reported that the cost effectiveness of various RZV vaccination strategies were highly subject to vaccine cost and the WTP threshold.[258] The second study concluded that RZV vaccination was more likely to be cost effective for the 60- to 70-year-old age groups than for age groups less than 60 years or over 70 years. They also noted that the age range for cost-effective acceptance of RZV vaccination appeared broader in females than males.[266] Of the three studies conducted for Japan, two reported consistent conclusions; one that vaccination with RZV at age 65 to 84 years should be considered when introducing an HZ immunisation programme[261] and the second that RZV vaccination would be cost effective for the Japanese population aged 65 years and older, compared with no vaccination.[264] The third study for Japan, that used an updated vaccine price, concluded that vaccination against HZ with RZV would be cost effective compared with no vaccination in the cohort of adults aged 65 years, with ICERs lower than those for a cohort vaccinated at aged 65 years and older.[271]

Of the five studies that assessed RZV and ZVL vaccination, one study conducted from the societal perspective in the US concluded that vaccination with RZV was more cost effective, versus no vaccination, than ZVL (based on lower ICERs), for all age groups studied. Additionally, the study concluded that RZV vaccination at age 50 years appears cost effective, versus no vaccination, at a WTP threshold of $100,000 per QALY gained.[259] In a second study conducted for the USA, authors concluded that vaccination with RZV yields cost-effectiveness ratios lower than those for many

recommended adult vaccines, including ZVL.[263] The study conducted from the healthcare system perspective for Canada concluded that RZV vaccination, compared with both no vaccination and vaccination with ZVL, would be cost effective in the Canadian population aged 60 years and older.[260] In the study for the Netherlands, conducted from the societal perspective, authors concluded that both RZV and ZVL vaccination strategies could be cost effective, with the most cost-effective alternative likely dependent on vaccine price.[256] The study conducted from the healthcare payer perspective in Belgium concluded that the cost effectiveness of RZV in 50 year-olds, versus no vaccination, would be dependent on vaccine price but that ZVL vaccination was never cost effective compared with RZV vaccination at WTP thresholds examined.[270]

5.7 Critical appraisal

Given that the objective of this rapid review was to assess the published international evidence on the approaches taken to modelling the expected costs and benefits of HZ vaccination, a critical appraisal of all included studies was undertaken using the framework for quality assessment of decision-analytic models proposed by Philips et al.[254] Overall, the appraisal did not raise major concerns with the quality of the included studies. However, within each of three domains assessed there were some concerns. In terms of the 'structure' domain, one study did not clearly state the perspective adopted and three studies selected time horizons (for example, 15 and 20) that may, depending on the age at vaccination, be considered too short when assessing the cost effectiveness of HZ vaccination. Additionally, one study did not account for waning immunity despite evidence of declining vaccine effectiveness. Within the 'data' domain, there were some concerns with regard to the level of detail provided for some parameter data, particularly with respect to utility weights and the calculation of QALY losses. Moreover, a number of studies did not provide sufficient detail on parameter data incorporated into the model, relying on referencing of past studies only. Lastly, the assessment of uncertainty was not considered comprehensive in a number of studies. Within the 'consistency' domain, a number of studies did not provide any description of model validation or internal consistency checks.

5.8 Discussion and comparison of results with most recently published systematic review

5.8.1 General and model characteristics

This rapid review provides an update of the evidence on the methodology of economic modelling of HZ vaccination since the most recently published relevant

systematic review by Chiyaka et al., which included studies published up until March 2018.[252]

Similar to the Chiyaka systematic review, most of the studies in this review were conducted for countries spread across Europe, North America, and the Asia-Pacific region. A similar percentage of studies were funded by industry in both reviews: 44% for the current review and 37% for the Chiyaka systematic review. A Markov model has been consistently used to model the cost effectiveness of HZ vaccination by the majority of studies in both the present review and the Chiyaka review (67% and 74%, respectively). The majority of studies that used Markov models in the current review adopted annual time cycles (83%), with just two studies (17%) using monthly cycles. However, in the Chiyaka review, 45% of studies that used a Markov model adopted a monthly time cycle, 30% used an annual cycle, 10% used a three-month cycle, while the remainder did not report cycle length. The majority of studies in both reviews adopted a lifetime time horizon and conducted the analysis from the societal perspective, with approximately half of these studies in both reviews also considering an alternative perspective.

5.8.2 Intervention and vaccination strategies

With the exception of a single study that assessed RZV vaccination, the 26 other studies in the Chiyaka systematic review assessed ZVL vaccination. This contrasts with the present review where the majority of studies (83%) assessed RZV vaccination alone or both RZV and ZVL vaccination strategies. The change in intervention assessed likely reflects the timeline for the authorisation of RZV (Shingrix®). Authorisation for Shingrix® was granted by the US Food and Drug Administration (FDA) in 2017[278] and by the European Medicines Agency (EMA) in March 2018.[279] Half of studies in the current review assessed vaccination in adults from 50 years of age in the base case analysis. In comparison, a minority of studies (n=5) in the previous systematic review assessed vaccination in adults aged from 50 years, with most of the reviews focusing on those aged 60 years and older.

5.8.3 Vaccine characteristics

The original RCTs of ZVL efficacy reported efficacy endpoints for HZ and PHN separately for those aged 60 years and older.[276] However, only two of nine studies assessing ZVL in the present review reported separate efficacy rates for herpes zoster and PHN.[268, 269] This compared with 22 of 27 studies in the Chiyaka review. All studies in the present review and most studies in the Chiyaka review that provided age-specific vaccine efficacy rates assumed lower efficacy in older age groups for both vaccines. Similar to the previous review, the duration of vaccine efficacy and waning immunity rates in the present review were not clearly reported

in a number of studies. Where these data were reported, they varied widely among studies in both reviews.

5.8.4 Costs and effects

The types of direct costs included in both reviews were generally consistent, including costs associated with GP and outpatient visits, medication, hospitalisation, vaccine and vaccine administration. However, a total of 12 of 18 (67%) studies included in the present review included the cost of vaccine-related adverse events, compared with seven of 27 studies (26%) in the earlier review. Productivity losses associated with HZ and PHN were included in both reviews where appropriate, that is, where the societal perspective was adopted.

Outcome measures included in studies in both reviews generally included herpes zoster and PHN cases, hospitalisation and HZ-related deaths. Health outcomes were measures in QALYs in all studies in the previous review and 17 of 18 studies in the present review. A total of 10 studies (56%) in the present review also considered non-PHN complications (e.g., ocular, neurological, cutaneous and cosmetic) in the model, compared with just 30% of the studies in the earlier review. However, data used to calculate QALY losses associated with non-PHN complications were generally poorly reported with only four studies in the present review reporting utility weights or QALY losses associated with non PHN-complications. Additionally, 12 studies (67%) in the current review included vaccine-related adverse events in the model, compared with approximately 33% of studies in the earlier review.

5.8.5 Conclusions from studies

The Chiyaka systematic review concluded that ZVL vaccination was cost effective, compared with no vaccination in many studies. However, the review also noted that a number of studies had variable conclusions depending on the vaccination strategy, chosen WTP thresholds, assumed duration of protection and age at vaccination. The Chiyaka review also reported that where RZV and ZVL vaccination were compared, RZV was dominant and when compared with no vaccination, RZV was cost effective. These findings were largely consistent with the results of the present review where RZV generally dominated ZVL and was cost effective compared with no vaccination. Additionally, a number of studies in the present review highlighted that the cost effectiveness of each RZV vaccination strategy was highly dependent on the vaccine cost and WTP threshold. While the earlier review noted that future studies should include other (non-PHN) long-term complications and vaccine-related adverse reactions, both of these outcomes have been included with greater frequency in the present review. Both reviews highlighted that clearer explanations and more detailed descriptions of model assumptions and estimated parameters are required.

5.9 Conclusion

The objective of this rapid review was to examine the approaches taken to modelling the expected costs and benefits of HZ vaccination in high-income countries and to use the findings to inform the economic modelling of herpes zoster vaccination for adults in Ireland. While a systematic review was identified that covered the period from database inception to March 2018 (earliest identified study published in 2001), this updated review provides an overview of the methodology of the economic modelling of herpes zoster vaccination over a 20-year period. The general approach to the economic modelling of HZ vaccination has not changed considerably over time, with overall methodologies, model structures and model assumptions generally consistent in both reviews. However, the present review identified that models are increasingly incorporating a larger number of health outcomes, including complications other than PHN and vaccine-related adverse events. The features highlighted in both reviews will be considered when developing the de novo economic model of HZ vaccination for Ireland.

6 Economic Evaluation

Key points

- An economic model was developed to estimate the cost effectiveness and budget impact of herpes zoster (HZ) vaccination for adults in the general population aged 50 years and older. The budget impact of HZ vaccination for a cohort of immunocompromised adults aged 18 years and older was also estimated.
- A closed-cohort Markov model approach was used to estimate the costs and outcomes associated with an HZ vaccination programme for adults in the general population aged 50 years and older. Eight alternative two-dose HZ vaccination strategies, with vaccination at 50, 55, 60, 65, 70, 75, 80 and 85 years of age, were assessed. Each strategy was based on vaccinating only those turning that age in a given year, rather than everyone that age and older.
- Model parameters including disease incidence rates, vaccine effectiveness, transition probabilities, costs and utility values were estimated from a variety of published sources and national datasets for Ireland.
- From both the payer and societal perspectives, the incremental cost-effectiveness ratios (ICERs) for all HZ vaccination strategies assessed in the general population, exceeded willingness-to-pay thresholds of €20,000 and €45,000 per quality-adjusted life-year (QALY) gained.
- At a vaccine cost of €151 per dose, the ICERs ranged from €127,825 per QALY for vaccination of 80-year-olds, to €979,815 per QALY for vaccination of 50-year-olds. Therefore, at this vaccine cost, HZ vaccination would not be considered cost effective. Based on the assumptions in the model, the vaccine cost would need to be less than €30.00 per dose for HZ vaccination at 75 and 80 years old to be cost effective at a willingness-to-pay threshold of €45,000 per QALY. The results of the economic evaluation were robust to probabilistic and one-way sensitivity analysis and various scenario analyses.
- The five-year incremental budget impact of an HZ vaccination programme for adults in the general population aged 50 years and older (with 50% coverage) ranged from €15.1 million with vaccination at 85 years old to €76.8 million with vaccination at 50 years old. Offering the vaccine to everyone over a certain age would incur a substantially larger budget impact than a single year of age. For

example, if everyone aged 65 years and over was offered the vaccine, the five-year budget impact based on 50% uptake would be €218 million.

- The five-year incremental budget for eligible immunocompromised persons (with 100% coverage), was estimated at €56.2 million. This estimate comprised €46.3 million for the cohort aged 50 years and older with non-specific immunocompromising conditions, €6.3 million for those with haematological malignancies, €2.2 million for solid organ transplant recipients, €745,000 for HSCT recipients and approximately €630,000 for those with advanced/untreated HIV. For all cohorts, the incremental budget impact in year one was significantly greater than years two to five as it was assumed that all those currently eligible for vaccination (the prevalent population) would be vaccinated in year one.
- As with any economic modelling exercise, there are limitations due to the quantity and quality of data available to populate the model. However, based on extensive scenario and sensitivity analyses, the findings are robust to data and structural assumptions.

6.1 Introduction

An economic model of herpes zoster (HZ) vaccination for adults in Ireland was developed as part of this HTA. This chapter describes the economic evaluation, comprising cost-utility and budget-impact analysis, to estimate the costs and benefits associated with the expansion of the immunisation schedule to include HZ vaccination for adults in the general population aged 50 years and older. Additionally, this chapter describes a separate budget-impact analysis (BIA) of HZ vaccination specifically for immunocompromised adults aged 18 years and older.

6.2 Methods

The analyses described in this chapter were conducted in line with national HTA guidelines,[183, 272, 280] reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[281] and undertaken in Excel 2016.

6.2.1 Study objective

The purpose of this health economic evaluation was to estimate the cost effectiveness and budget impact of an HZ vaccination programme for adults in the general population aged 50 years and older and the budget impact of an HZ vaccination programme for immunocompromised adults in Ireland. The cost-utility

analysis (CUA) estimates the costs and outcomes of HZ vaccination compared with no vaccination, while the budget impact analysis (BIA) provides a means of predicting the potential financial impact of introducing an HZ vaccination programme.

6.2.2 Target population

HZ results from reactivation of the varicella zoster virus (VZV). The individual lifetime risk of developing HZ in those with a history of varicella is approximately 30% (Chapter 3). The target population for an HZ vaccination programme for adults in the general population is those aged 50 years and over. For the economic evaluation, the target population comprised a closed cohort of 50-year-old adults.

The target population for an HZ vaccination programme for immunocompromised adults aligns with HZ immunisation recommendations from NIAC that include the following individuals (Chapter 3):

- haematopoietic stem cell transplantation (HSCT) recipients, aged 18 years and over
- solid organ transplant recipients, those with haematological malignancies and those with advanced or untreated HIV (CD4 count <200 cells/µl), aged 18 to 49 years
- those with non-specific immunocompromising conditions, aged 50 years and older.

6.2.3 Intervention

The model assessed a primary-care based, two-dose HZ vaccination programme, with the vaccine administered either in the GP practice or pharmacy setting (section 7.5). A number of mutually exclusive strategies were assessed that assumed vaccination at a specific age. Catch-up and mop-up vaccination programmes were not considered in the analysis. The full set of included vaccination strategies for the general population aged 50 years and older was vaccination at:

- 50 years old
- 55 years old
- 60 years old
- 65 years old
- 70 years old
- 75 years old

- 80 years old
- 85 years old.

6.2.4 Comparator

The comparator in both the CUA and BIA was no vaccination. It is noted that the HZ vaccine can be purchased privately in Ireland. However, it is believed that uptake is low (<0.5% of those aged 50 years and over (Chapter 7)) and including this small number of vaccinated individuals in the model would have a negligible impact on the results of the economic evaluation.

6.2.5 Study design

A CUA was undertaken to estimate the incremental cost and health benefits associated with HZ vaccination for adults in the general population aged 50 years and older, relative to no vaccination. Health benefits were expressed in terms of quality-adjusted life-years (QALYs), which reflect the impact of the intervention on patients' quality and quantity of life. The analysis was undertaken within a decision-analytic framework that simulated the long-term costs and patient outcomes associated with HZ.

The BIAs estimated the incremental cost to the HSE of implementing HZ vaccination programmes for both adults in the general population aged 50 years and older and immunocompromised adults over a five-year time horizon.

6.2.6 Model structure

A closed-cohort Markov chain simulation model was developed to compare no vaccination with HZ vaccination for adults in the general population aged 50 years and older, in terms of both costs (in Irish Euro) and outcomes (QALYs). The model comprised the following health states:

- healthy
- vaccinated
- HZ
- post-herpetic neuralgia (PHN) following initial HZ
- recovered
- recurrent HZ
- PHN following recurrent HZ

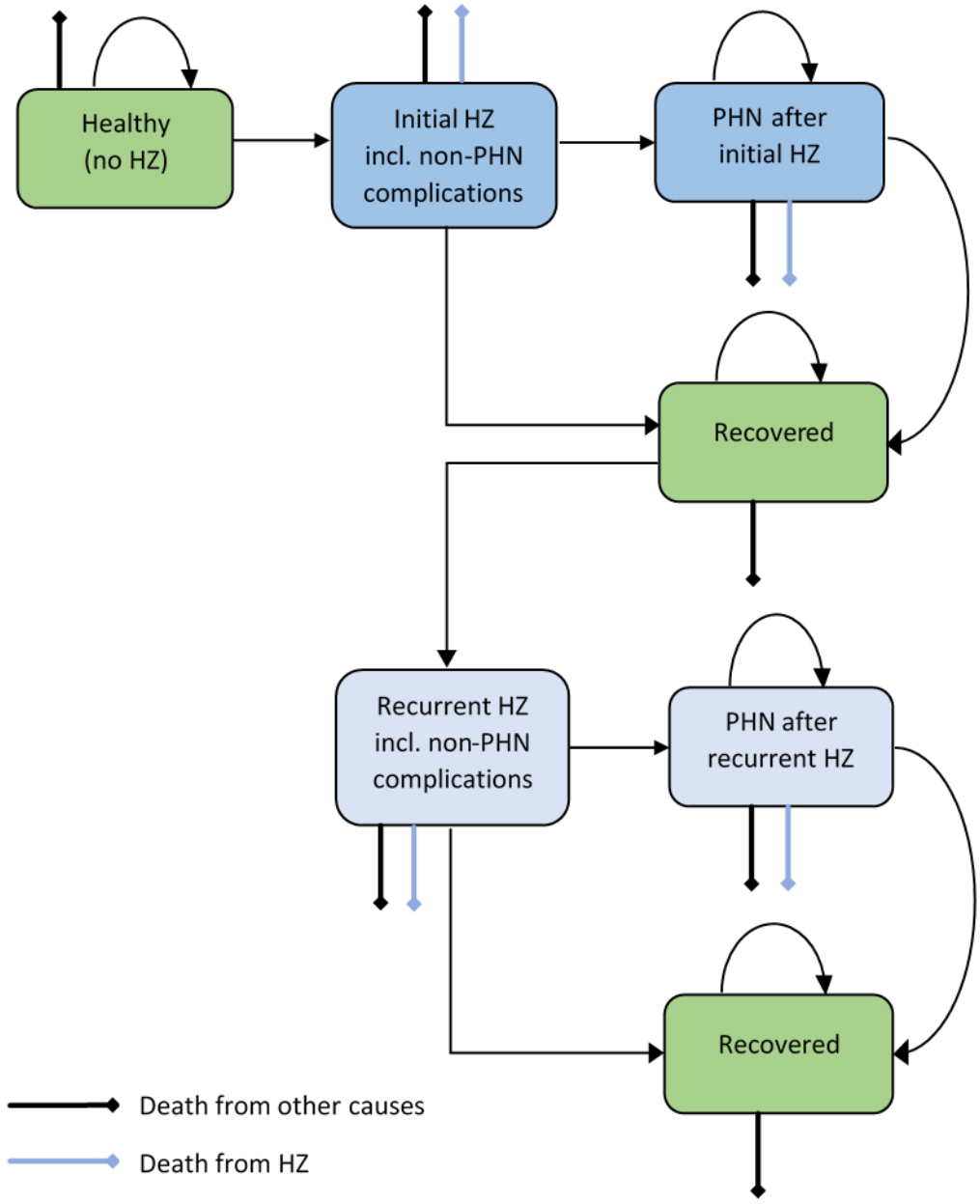
- death.

The cohort enters the model in the healthy state after which they move through the model in one-month cycles. A schematic of the Markov model, which illustrates the possible pathways through the model, is presented in Figure 6.1.

In the absence of vaccination, it was assumed that those in the healthy state were susceptible to HZ. Individuals that developed HZ could develop complications requiring hospitalisation and or develop PHN. Following recovery from initial HZ, the model assumed individuals could develop recurrent HZ once only. Following vaccination, the cohort moved to the vaccinated health state where their susceptibility to HZ was reduced in line with vaccine effectiveness, but taking consideration also of waning immunity rates. Similar to the unvaccinated cohort, vaccinated individuals who developed HZ could develop complications requiring hospitalisation and or develop PHN. Following recovery from initial HZ, vaccinated individuals could develop recurrent HZ once only. In line with the findings on the safety of HZ vaccination from Chapter 4, it was assumed that non-serious adverse events were a possible outcome following vaccination. Costs and QALYs were assigned to all health outcomes for both the no vaccination and vaccination cohorts, enabling the calculation of the incremental costs and incremental QALYs associated with HZ vaccination.

The BIAs were both designed as open-cohort models. For the cohort of adults in the general population aged 50 years and older, new cohorts were eligible for HZ vaccination each year for five years of the BIA. The BIA model for the general population also included cost savings (primary care and hospitalisation) as a result of vaccination. For the immunocompromised cohort, the prevalent population was eligible for HZ vaccination in year one, with the incident population eligible in each of the subsequent four years of the BIA. Given the uncertainty about the risk of HZ and PHN in the immunocompromised cohort and the age at which it occurs, the potential costs averted as a result of a decrease in incidence of disease and reduced need for zoster prophylaxis associated with the introduction of a vaccination programme have not been included in the BIA. The net budget impact per annum and total budget impact over five years were estimated, defined as the difference in average annual costs between vaccination and no vaccination.

Figure 6.1 Schematic representation of model structure



Key: HZ – herpes zoster; PHN – post-herpetic neuralgia

6.2.7 Perspective, time horizon and discounting

In the base-case analysis, the CUA adopted the perspective of the Irish publicly funded health and social care system (that is, the payer), namely the HSE. In line with recommended good practice guidelines for the economic analysis of vaccination programmes and given the expected impact on productivity, a societal perspective was also adopted.[282] For the payer perspective, only direct medical costs to the HSE were incorporated. For the societal perspective, direct medical costs to the HSE, indirect costs such as productivity losses associated with morbidity for individuals

with the disease, out-of-pocket expenses incurred by individuals for GP visits and medication, and opportunity costs associated with publicly funded GP care, were included in the analysis. Costs and benefits were estimated over a 50-year time horizon, and discounted at a rate of 4% as specified in national guidelines.[272] Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. In the BIAs, the incremental costs associated with introducing an HZ vaccination programme were estimated over a five-year time horizon. To reflect the actual cost to the HSE in each year reported, and ensure consistency with national guidelines,[280] no discounting was applied.

6.2.8 Model input parameters

Incidence rates, probabilities, costs and utility values were estimated from a variety of published sources and national datasets for Ireland, including those published by the Central Statistics Office (CSO), the Healthcare Pricing Office (for Hospital In-Patient Enquiry (HIPE) data), and the Health Protection Surveillance Centre. These sources were supplemented by input provided by experts where necessary. For the CUA, 50% vaccination coverage was assumed. In addition, it was assumed that no capital investment would be required for an HZ vaccination programme and that promotion and training costs would be proportional to vaccination costs. Given the assumptions related to programme costs and the fact that the risk of transmission of VZV from those with HZ to those susceptible to varicella is low, any variation in the uptake rate would have limited impact on the difference in costs and QALYs between the intervention and comparator and therefore the results of the CUA. For the purpose of the BIA, 50% coverage was also assumed in the base-case analysis.

Model inputs were selected with consideration to the hierarchy of evidence, as well as generalisability to the Irish context. Inputs for the BIAs were consistent with those used in the CUA with the exception of the addition of VAT (where applicable). However, only direct costs were included and indirect costs, such as productivity gains associated with reduced morbidity arising from vaccination, were excluded from the BIAs.

All economic model input parameters are provided in Appendix C 6.1.

6.2.9 Health outcomes

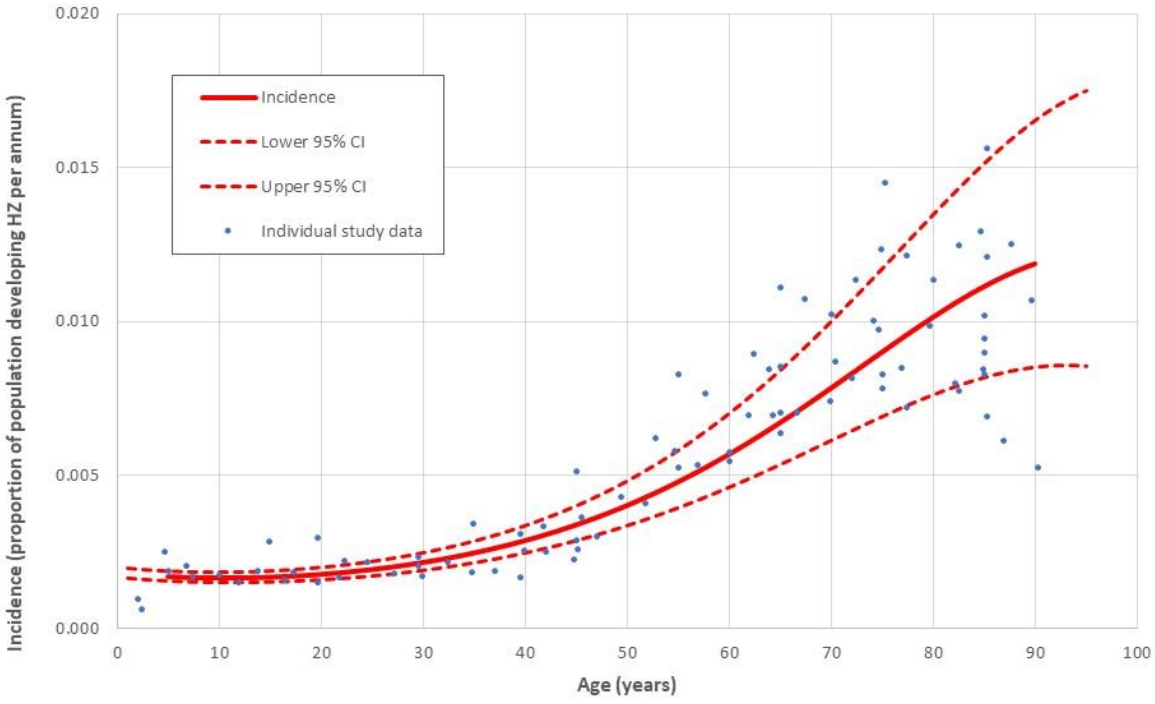
In the Markov model, movement between health states (that is, disease progression) was governed by transition probabilities. As the model uses a one-month cycle length, annual transition probabilities and instantaneous event rates from published literature sources were converted to one-month probabilities of event occurrence. This method assumes that the event rate is constant over time.[283]

6.2.9.1 Incidence of disease

The presentation of HZ in the community in Ireland was estimated from case data obtained from the sentinel surveillance programme for HZ.[98] However, these data do not capture those who have HZ in the community and who do not present at the GP, and are therefore likely to be an underestimate of the true incidence. In order to obtain an accurate estimate of the disease burden in Ireland, international HZ incidence data[6] were used to estimate age-specific (by single year of age) annual incidence rates (Table 6.2) using the following equation:

$$HZ\ incidence\ rate = \frac{\exp(-6.30 + (age * -0.019) + (age^2 * 0.00101) + (age^3 * -0.000006))}{1 + \exp(-6.30 + (age * -0.019) + (age^2 * 0.00101) + (age^3 * -0.000006))}$$

Figure 6.2 Estimated herpes zoster incidence for Ireland by age



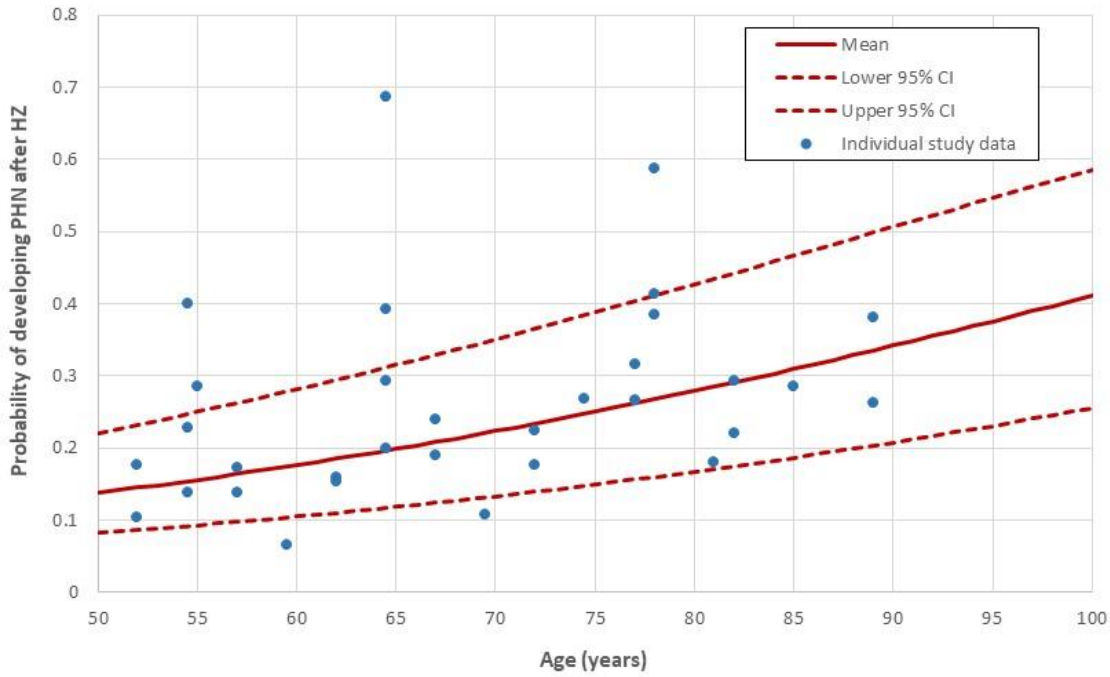
Key: HZ – herpes zoster

Using international data on incidence and duration of PHN,[119, 123-125, 284-286] the probability of developing PHN in the month following HZ (Figure 6.3) and the monthly probability of recovering from PHN (by single year of age) were estimated using the following equations:

$$Probability\ of\ PHN = \frac{\exp(-3.30588 + (age * 0.029459))}{1 + \exp(-3.30588 + (age * 0.029459))}$$

$$Probability\ of\ recovery\ from\ PHN = 0.2762 + (age * -0.0014)$$

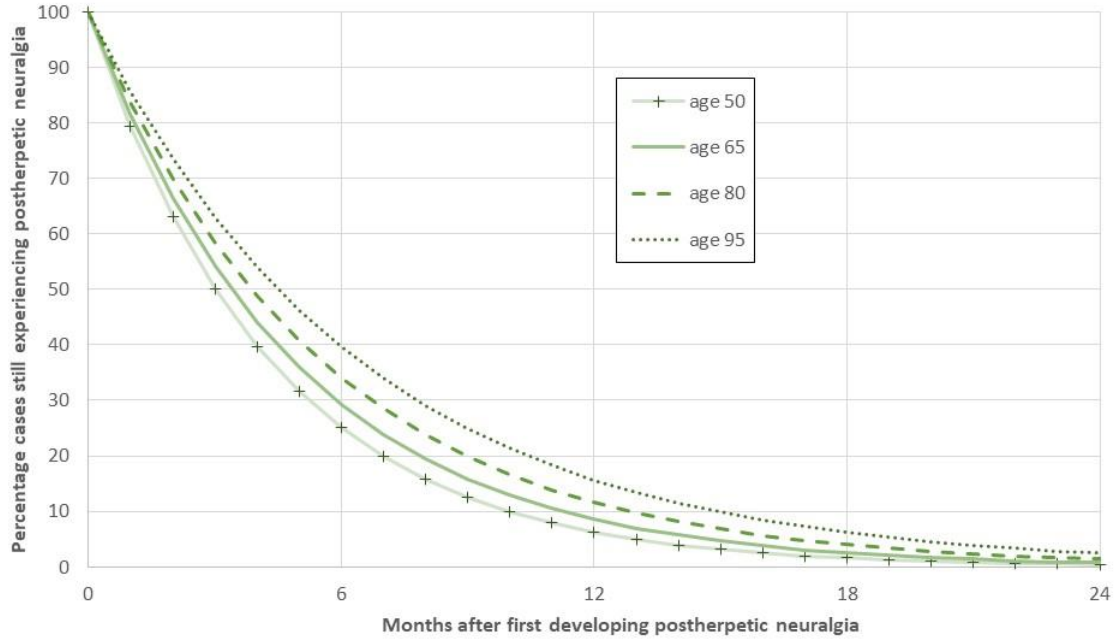
Figure 6.3 Estimated probability of developing post-herpetic neuralgia by age



Key: PHN - post-herpetic neuralgia; HZ - herpes zoster

Figure 6.4 illustrates the model estimate of the percentage of initial PHN cases that continue to experience PHN symptoms over time (for example, 30% of 65-year-olds that develop PHN still experience symptoms six months later).

Figure 6.4 Estimated percentage of initial post-herpetic neuralgia cases that continue to experience symptoms over time, by age



In the absence of strong evidence to the contrary, the risk of developing recurrent HZ was assumed to be the same as that for initial HZ. HZ-related mortality data were obtained from HIPE discharge data and all-cause mortality rates were obtained from the CSO.[287]

6.2.9.2 Primary care resource use

Based on the results of an Irish study, exploring the frequency of diagnosis and cost of acute HZ and PHN in the community, an average GP consultation rate was applied to all HZ and subsequent PHN cases.[108]

6.2.9.3 Probability of hospitalisation

The probability of hospitalisation for HZ was estimated from HIPE discharge data for the years 2017 to 2022 inclusive, excluding 2022 due to the impact of COVID-19 on overall hospitalisations (Table 6.1). These data included the total number of inpatient and day case discharges with a primary diagnosis of B02X Zoster (herpes zoster) per the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM),[288] by age group and year.

Table 6.1 Estimated probability of a herpes zoster case requiring hospitalisation

Age group (years)	Estimated mean probability of an HZ case requiring hospitalisation	95% CI
50-54	0.96%	0.52% - 1.52%
55-59	0.95%	0.53% - 1.49%
60-64	1.45%	0.93% - 2.08%
65-69	1.65%	1.10% - 2.30%
70-74	2.02%	1.41% - 2.75%
75-79	2.20%	1.51% - 3.01%
80-84	4.53%	3.34% - 5.89%
≥85	4.52%	3.31% - 5.91%

Key: CI – confidence interval; HZ – herpes zoster

6.2.9.4 HZ vaccine efficacy/effectiveness

The assessment of vaccine effectiveness against HZ (Chapter 4) reported vaccine efficacy in the general adult population aged 50 years and older of 92% from combined RCT data and vaccine effectiveness of 72% from observational data. It also reported RCT data from one long-term follow-up study in this population showing that vaccine efficacy wanes from an initial 97.7% to 73.2% by year 10. The available observational data was based on a much larger sample size (33 million person-years) than the RCT data (29,311 person-years), and the risk of HZ was more aligned to international incidence data. For the purpose of the CUA, a conservative approach was adopted where the observational vaccine effectiveness data were used in the base-case model. A waning immunity rate of 2.54 percentage points per annum was applied, derived from a linear regression of the published trial data reported in Chapter 4.

The assessment of vaccine effectiveness against PHN (Chapter 4) reported that, based on RCT data, there was no difference in the risk of PHN for those with HZ. However, based on the observational study results there was a protective effect against PHN for those with HZ who had been vaccinated (RR 0.39, 95% CI 0.30 to 0.50). In the base-case model, a risk-ratio parameter was included to adjust the risk of PHN in those vaccinated.

6.2.9.5 HZ vaccine safety

Overall evidence from the assessment of the safety of HZ vaccination (Chapter 4) suggests that HZ vaccination is safe and, while mild local and systemic reactions are relatively common, serious adverse events are uncommon. For the purpose of the CUA it was assumed that 14% of all HZ vaccinations result in Grade 3 adverse events that require a GP visit. Given that the RCT data demonstrated similar incidence of serious adverse events in vaccine and placebo groups, these were not included in the model.

6.2.9.6 Quality of life estimates

In the model, health benefits are expressed in terms of quality-adjusted life-years (QALYs) gained. QALYs reflect the impact of an intervention on patients' quality and length of life, estimated using self-reported utilities or health-related quality of life.

The cohort was assigned Irish baseline utility values (by age group) at the outset of the model.[141] Each health state was associated with different health utilities to capture the impact of that state on health-related quality of life. A comprehensive search was conducted to identify original studies that elicited health-state utility values or disutilities associated with HZ and PHN.[289] Preference was given to utility values measured using generic preference-based measures such as the EQ-5D. Studies measuring different pain states associated with HZ or PHN using the EQ-5D tool[113, 290-293] were excluded due to the uncertainty involved in weighting health states for HZ and PHN based on severity of pain and in the absence of Irish data to support this calculation. Four studies were excluded due to the use of three different measurement tools.[294-297] This conservative approach is in line with Irish guidelines[272] that advise that utilities derived using different techniques may systematically differ.[298] The utility values from the included studies[137-140, 241, 299-303] were assigned to the midpoint of the reported age bands and a linear fit was used to estimate the relationship between age and utility. For HZ and PHN, utility values decreased with increasing age. This may partly reflect increasing disutility with age, but also the fact that baseline utility values also decrease with age.

The baseline and health-state utility values used to estimate QALYs in the CUA are presented in Table 6.2.

For the purpose of the CUA, the utility loss associated with adverse events following vaccination was assumed to be the same as that for HZ. Based on the findings in Chapter 4 relating to the transient nature of reactions to the vaccine, this disutility was assumed to last for one day.

Table 6.2 Baseline and health-state utility values

Age group (years)	Baseline*	HZ		PHN	
		Mean	95% CI	Mean	95% CI
50-54	0.910	0.799	0.752 – 0.842	0.792	0.744 – 0.836
55-59	0.900	0.788	0.740 – 0.832	0.765	0.715 – 0.810
60-64	0.900	0.777	0.728 – 0.822	0.737	0.686 – 0.785
65-69	0.880	0.766	0.716 – 0.812	0.710	0.657 – 0.759
70-74	0.880	0.755	0.705 – 0.802	0.682	0.628 – 0.733
75-79	0.840	0.744	0.693 – 0.791	0.655	0.600 – 0.707
80-84	0.840	0.733	0.681 – 0.781	0.627	0.572 – 0.681
≥85	0.840	0.721	0.669 – 0.770	0.597	0.541 – 0.652

Key: CI – confidence interval; HZ – herpes zoster; PHN – post-herpetic neuralgia
*Source: Irish baseline utility values – Hobbins et al.[141]

6.2.9.7 Cost inputs

In accordance with national HTA guidelines, all costs are presented in 2023 Irish Euro (€).[272] All costs were derived from Irish sources and those from years prior to 2023 were adjusted using the Consumer Price Index (CPI).[304]

In the CUA, the costs associated with HZ and PHN from the payer perspective included the cost of GP visits for those with a GP visit or medical card, the cost of medication for those with a medical card and the cost of hospitalisation. The proportion of people with a GP visit and or medical card was sourced from HSE - Primary Care Reimbursement Service eligibility data as at November 2023 (Table 6.3).[305] The total cost of primary care visits and medication for acute HZ and PHN were sourced from an Irish study exploring the frequency of diagnosis, methods of treatment and costs in primary care.[108] The average cost per case of HZ and PHN (Table 6.4) were inflated to 2023 Irish € using the *Doctor's fees* and *Prescribed drugs* sub-indices of the CSO's CPI monthly series data.[304]

Table 6.3 Estimated proportion of the population eligible for a GP visit card or a medical card

Age group (years)	Proportion of population eligible for a GP visit card*	Proportion of population eligible for a medical card*
50-54	3.1%	25.7%
55-59	2.5%	30.9%
60-64	2.5%	30.9%
65-69	2.8%	38.8%
70-74	34.9%	57.2%
75-79	23.1%†	76.9%
80-84	23.1%†	76.9%
≥85	23.1%†	76.9%

*This figure was adjusted from 27.5% to ensure that the total proportion of the population eligible for a GP visit card or medical card in these age groups did not exceed 100%.
†Source: Health Service Executive[305]

Table 6.4 Average primary care costs for a case of acute herpes zoster and for post-herpetic neuralgia

Average cost	Acute herpes zoster*	Post-herpetic neuralgia*
GP visit	€117.65	€125.73
Medication	€81.51	€79.38

*Source: Crosbie et al.[108]

The average hospitalisation cost for a case of HZ, by age group, (Table 6.5) was estimated based on the total number of HIPE discharges with a primary diagnosis of B02X Zoster (herpes zoster) per (ICD-10-AM) for the five-year period 2017 to 2022, excluding 2020 due to the impact of COVID-19 on overall hospitalisations.[306] Discharge data were split into the following three most common Diagnostic Related Groups (DRGs) for an HZ diagnosis:

- B72B Nervous System Infection Except Viral Meningitis, Minor Complexity
- C60B Acute and Major Eye Infection, Minor Complexity

- J68A Major Skin Disorders, Major Complexity.

Discharges with a primary diagnosis of B02X Zoster (herpes zoster) and not classified as either B72B, C60B or J68A, were classified as 'Other'. Discharge data were reported by age, length of stay, and the associated DRG prices as published by the HPO.[307] The estimated DRG price for those discharges classified as 'Other' was calculated as a weighted average of the other three DRG prices. The costs provided in Table 6.5 are estimated average costs and individual cases could incur higher or lower costs depending on the intensity of treatment and length of stay (LOS). While average LOS is greater for older age groups, the average LOS for all age groups for each of the DRGs lies within the lower and upper LOS boundaries for activity-based funding and therefore all are classified as inliers for the calculation of the monetary value of a hospitalised case.

Table 6.5 Estimated average hospitalisation cost for a case of herpes zoster

Age group (years)	Estimated average hospitalisation cost for a case of herpes zoster*
50-54	€5,870
55-59	€6,134
60-64	€5,477
65-69	€6,082
70-74	€6,137
75-79	€6,167
80-84	€5,930
≥85	€5,917

*Source: Healthcare Pricing Office[306, 307]

In addition to the costs included in the payer perspective (described above), the societal perspective also included the following costs for HZ and PHN:

- out-of-pocket expenses for those not eligible for a GP visit or medical card and who therefore incur GP consultation and prescription medication costs. Transport costs incurred to attend the GP were not included.
- productivity loss of paid work, due to absenteeism, for those who are ill.

The proportion of the population not eligible for a GP visit or medical card (and therefore considered private patients) was determined based on scheme eligibility data published by the HSE (Table 6.3).[305] The average cost of GP consultations and

prescription medication for private patients with HZ and PHN was assumed to be the same as that described above for the payer perspective.

Absenteeism relating to HZ and PHN is mostly reported during the acute phase of HZ.[153] Therefore, estimates of the productivity loss to society of paid work included in the model were limited to absenteeism for HZ. Productivity loss was valued using the Human Capital Approach by multiplying the days lost to health problems by median daily earnings.[308] The average number of work days lost per case of HZ was sourced from the literature and was assumed to be four.[153-155] Labour force data published by the CSO were used to estimate the proportion of the population in paid employment for each age group of the model (Table 6.6).[309] Earnings analysis data published by the CSO[310] were used to estimate median daily earnings (in 2023) by age group (Table 6.6).

Table 6.6 Proportion of the population in paid employment and estimate of median daily earnings by age group

Age group (years)	Percentage of the population working	Estimate of median daily earnings
50-54	83.4%	€160.14
55-59	74.6%	€160.14
60-64	61.0%	€124.14
65-69	25.0%	€124.14
70-74	15.0%	€124.14
75-79	9.5%	€124.14
80-84	0%	N/A
≥85	0%	N/A

Key: N/A – not applicable

6.2.9.8 Vaccination programme costs

For both the payer and societal perspectives, HZ vaccination programme costs included procurement, administration, national cold chain service (that is, storage and transportation of the vaccines), as well as education and communication about the HZ vaccination programme. The cost of the vaccine to the healthcare system (which could, for example, include a volume discount) is not known. Based on the vaccine price used in the studies assessed in the rapid review of modelling studies (Chapter 5), and the advertised cost for private vaccination in Ireland, a vaccine price of €151.00 (excluding VAT) per dose was assumed in the base-case scenario.

The cost for administration of one vaccine dose was assumed to be €25.00. This is in line with the administration fee payable to pharmacists for administering a COVID-19 vaccination for winter 2023/2024.[311] The costs of national cold chain service and education and communication about the HZ vaccination programme were assumed to be 3.9% and 1.5% of the total vaccine procurement cost, respectively. These figures were estimated based on historic national immunisation expenditure data.[312]

6.2.10 Model outputs

In the CUA, incremental costs and QALYs were estimated and then used to calculate a cost-effectiveness ratio — the incremental cost per QALY gained. In the first instance, all vaccination strategies were compared with no vaccination to estimate an average cost-effectiveness ratio (ACER). The strategies were then ordered by increasing cost and compared with the next least costly alternative to estimate an incremental cost-effectiveness ratio (ICER). In accordance with national HTA guidelines, the ICERs were reported relative to willingness-to-pay (WTP) thresholds of €20,000 and €45,000 per QALY.[272] For the BIA, incremental costs associated with, and costs averted as result of the introduction of a vaccination programme, were estimated and used to calculate the budget impact over five years.

6.2.11 Assessment and quantification of uncertainty

Probabilistic and deterministic sensitivity analyses (PSA and DSA, respectively) were conducted to test the robustness of the economic model outputs.

6.2.11.1 Sensitivity analysis for cost-utility analysis

Parameter uncertainty was assessed using a Monte Carlo simulation with 10,000 iterations. Each model parameter was defined by a statistical distribution to represent uncertainty in the mean parameter value. For each parameter, an appropriate statistical distribution was selected (for example, a beta distribution for a probability). Parameter values were then drawn as random variates from their specified distributions and the total costs and benefits were recalculated.

The total costs and QALYs for each simulation were recorded and used to quantify the proportion of simulations that were considered cost effective with respect to the cost-effectiveness threshold (that is, €45,000 per QALY). The output was presented on a cost-effectiveness plane. While there is no specific guidance available on the optimal number of simulations necessary to reach convergence,[313] model convergence was assessed to ensure convergence was reached after 10,000 simulations.

One-way sensitivity analysis (OWSA) for each vaccination strategy was conducted by fixing each parameter in turn at its upper and lower bounds, while all other

parameters were held at the mean. The impact of extreme variation in single-input parameters on the model output was presented on a tornado plot. This provides a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters.

6.2.11.2 Scenario analysis for cost-utility analysis

In developing the economic model, a number of important assumptions were made regarding both structural and parameter uncertainty. Scenario analyses were conducted to assess these uncertainties, whereby model assumptions and base-case parameter values were systematically varied. The following scenarios were modelled:

- *Scenario 1:* the base-case parameter value for vaccine effectiveness was based on a meta-analysis of RZV effectiveness data from observational studies only (Chapter 4). Based on the observational data, the base-case analysis also included a reduction in risk of PHN in those vaccinated, but who subsequently develop HZ. A scenario analysis was conducted where the parameter value for vaccine effectiveness was based on a meta-analysis of RZV effectiveness data from RCTs only. Consistent with the RCT evidence, this scenario analysis did not include a reduction in risk of PHN in those vaccinated, but who subsequently develop HZ.

- *Scenario 2:* in the base-case scenario, it was assumed that the cost of HZ vaccine administration for all individuals would be borne by the health and social care system. However, currently in Ireland, an individual may be required to pay the vaccine administration fee for recommended and funded adult vaccines (as in the case of the pneumococcal vaccine). A scenario analysis was conducted where it was assumed that the health and social care system would only cover the vaccine administration fee for those with a medical card or GP visit card.

- *Scenario 3:* in the base-case analysis conducted from the societal perspective, productivity losses due to absence from paid work were limited to those with HZ only. A number of studies reviewed in Chapter 5 reported productivity losses associated with PHN. However, there was considerable variation in the number of work hours or days lost reported, as well as quality issues with reporting of data, including detail regarding the data source.[259, 264, 265, 271, 314, 315] As this presented difficulties for application to the Irish setting, a scenario analysis was conducted that also included productivity losses associated with absence from paid work for those with PHN.

- *Scenario 4:* given that a CUA was not conducted for the immunocompromised cohort, a scenario analysis was conducted to explore the impact of an increased risk of HZ on the cost effectiveness of vaccination. As noted in Chapter 3, specific immunocompromised groups have an elevated risk of HZ and the level of increased risk depends on the subgroup. Individuals who have undergone solid organ transplant or HSCT tend to have a mean age of just over 50 years, while those with HIV tend to be younger. In the base-case analysis, the incidence of HZ at two years for 50-year-olds was 8.2 per 1,000 person-years. For individuals who have undergone solid organ transplant, the expected incidence of HZ is between 14 and 41 per 1,000 person-years, depending on the type of transplant.[107] For those who have undergone HSCT, the expected incidence is between 60 and 90 per 1,000 person-years.[106, 316, 317] For individuals with HIV, a German study estimated that the risk was 4 to 11 times that of the equivalent general population.[318] In the base-case model, that increased risk would equate to an incidence of between 32 and 88 per 1,000 person-years.

  In addition to the elevated risk of HZ, there is the issue of how long that increased risk is sustained for. A study of individuals that have had HSCT found that the elevated risk was concentrated in the first year after the procedure.[106] For this scenario analysis, we examined the impact of a linear return to general population risk of HZ over two years, five years and 10 years.

  Based on RCT evidence, vaccine efficacy is lower in immunocompromised groups.[200] For this scenario analysis, vaccine effectiveness based on observational evidence was modelled as 0.66 to reflect the lower effectiveness in immunocompromised individuals.[200]

6.2.11.3 Threshold analysis for cost-utility analysis

A threshold analysis estimates the conditions above or below which the model output may become cost effective, by substituting the point estimate for a wide sequence of values and recording the variation in model outputs. Given the uncertainty around the cost of the vaccine, it was assessed by threshold analysis.

6.2.11.4 Sensitivity analysis for budget-impact analysis

One-way sensitivity analysis (OWSA) was conducted by fixing each parameter in turn at its upper and lower bounds, while all other parameters were held at the mean. The impact of extreme variation in single input parameters on the model output was examined to assess the sensitivity of the model to the uncertainty associated with individual parameters.

6.2.11.5 Scenario analysis for budget-impact analysis

In developing the economic model, a number of important assumptions were made regarding parameter uncertainty. Scenario analyses were conducted to assess these uncertainties, whereby base-case parameter values were varied. The following scenarios were modelled for the BIA:

- *Scenario 1:* for both BIAs, scenario analyses were conducted where the cost of the vaccine was varied beyond the +/- 20% conducted in the OWSA
- *Scenario 2:* given that there is a high degree of uncertainty with regard to the number of people with immunocompromising conditions that may be eligible for HZ vaccination, a scenario analysis was conducted in the BIA where the number of people with non-specific immunocompromising conditions was adjusted. This adjustment was based on HPSC data that details the number of people aged 50 years and older with a medical risk condition that received the seasonal influenza vaccine in the 2022-2023 season.

The base-case analysis was conducted based on eligibility for HZ vaccination at specified ages from 50 to 85 years old inclusive. Two scenario analyses were conducted to estimate the potential budget impact of offering HZ vaccination to all adults aged 65 years and older and all adults aged 85 years and older.

6.2.12 Model validation and calibration

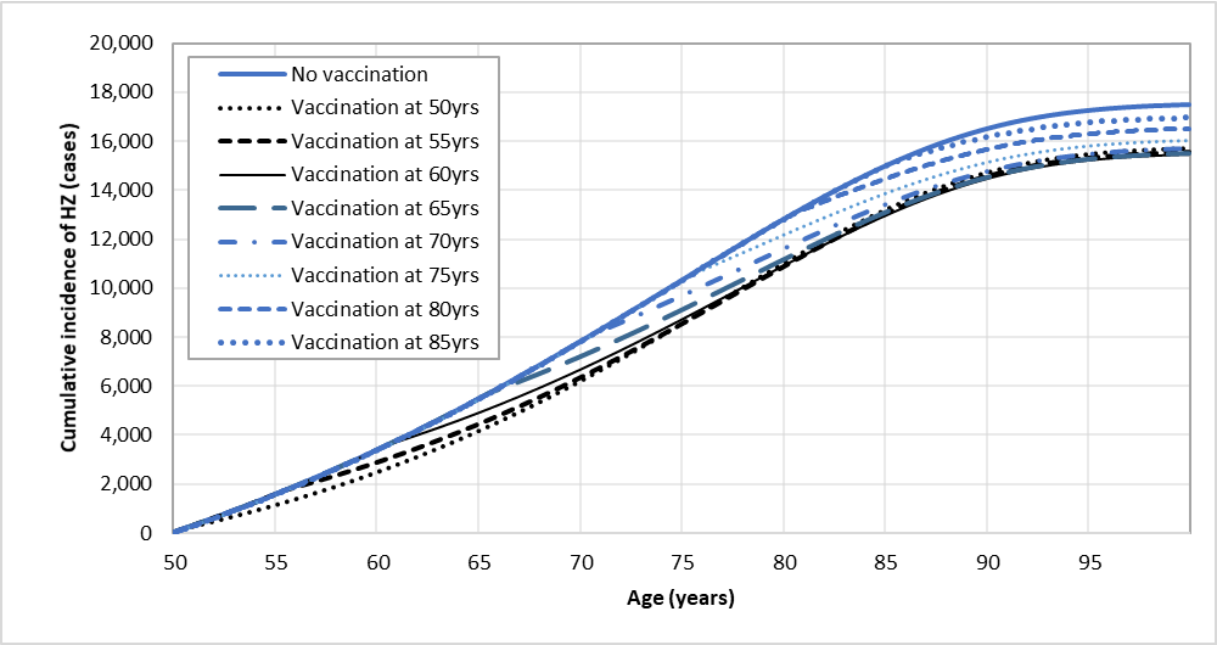
Internal validation of model was conducted in accordance with HIQA's Internal Quality Assurance Framework. All model inputs, calculations, and model outputs were reviewed by a second economic modeller.

6.3 Results

6.3.1 Epidemiological analysis

The incidence and prevalence of HZ disease in Ireland generated by the model from age 50 years onwards before vaccination, approximated incidence and prevalence in Ireland estimated using international data (Figure 6.5).

Figure 6.5 Estimated cumulative incidence (cases) of herpes zoster from age 50 years, with and without vaccination (50% coverage)



Following the introduction of HZ vaccination and assuming a 50% coverage rate, the reduction in the absolute number of cases of HZ and PHN varied by age at vaccination. With vaccination at 85 years of age, the estimated cumulative reduction in HZ cases in the 10 years following vaccination for the cohort aged 85 to 94 years old inclusive, was 494 cases (from 2,287 to 1,793). With vaccination at both 65 and 70 years old, the estimated cumulative reduction in HZ cases in the 10 years following vaccination for the cohorts aged 65 to 74 years old and 70 to 79 years old was 1,213 cases (from 4,845 to 3,632 cases and from 5,001 to 3,788 cases, respectively) (Table 6.7).

Table 6.7 Herpes zoster cases prevented with vaccination (in cumulative cohorts in the 10 years following vaccination)

Year following vaccination \ Age at vaccination	50yrs	55yrs	60yrs	65yrs	70yrs	75yrs	80yrs	85yrs
1	42	48	54	60	63	63	56	41
2	143	164	185	203	214	210	184	132
3	243	279	314	344	360	351	302	211
4	343	392	441	482	501	483	410	279
5	441	504	566	615	637	608	507	336
6	538	614	688	745	766	724	593	384
7	633	722	806	870	889	831	669	422
8	727	828	921	990	1,004	928	735	452
9	819	930	1,033	1,104	1,112	1,016	791	476
10	908	1,030	1,140	1,213	1,213	1,095	837	494

With vaccination at 50 years old, the estimated cumulative reduction in PHN cases in the 10 years following vaccination was 130 cases (from 480 to 350) in the cohort aged 50 to 59 years old. With vaccination at 70 years old, the estimated cumulative reduction in PHN cases in the 10 years following vaccination was 264 cases (from 1,098 to 834) in the cohort aged 70 to 79 years old (Table 6.8).

Table 6.8 Post-herpetic neuralgia cases prevented with vaccination (in cumulative cohorts in the 10 years following vaccination)

Year following vaccination \ Age at vaccination	50yrs	55yrs	60yrs	65yrs	70yrs	75yrs	80yrs	85yrs
1	4	6	7	9	10	11	11	9
2	18	23	29	35	41	45	43	34
3	31	40	51	62	72	77	73	56
4	45	58	73	88	102	108	101	75
5	59	76	95	115	131	138	126	92
6	73	93	117	141	160	167	150	106
7	87	111	139	166	188	193	171	117
8	101	129	160	191	215	218	189	126
9	116	147	182	216	240	241	205	134
10	130	165	203	240	264	262	218	139

Following the introduction of HZ vaccination and assuming 50% coverage, the predicted reduction in HZ cases over the time horizon of the model ranged from 12% when vaccination commenced at 60 or 65 years old to 3% when vaccination commenced at 85 years old (Table 6.9).

Table 6.9 Estimated change in herpes zoster (cases and %) by age group and age at vaccination with 50% coverage, compared with no vaccination

Age at vaccination (years) \ Age group for HZ	50-59yr olds	60-69yr olds	70-79yr olds	80-89yr olds	≥90yr olds	Total
50	-908	-700	-184	17	6	-1,769
	-27%	-16%	-4%	0%	1%	-10%
55	-504	-964	-468	-10	7	-1,939
	-15%	-22%	-9%	0%	1%	-11%
60	0	-1,1400	-758	-144	7	-2,035

Age group for HZ / Age at vaccination (years)	50-59yr olds	60-69yr olds	70-79yr olds	80-89yr olds	≥90yr olds	Total
	0%	-26%	-15%	-4%	1%	-12%
65	0	-615	-1,039	-345	-4	-2,004
	0%	-14%	-21%	-9%	0%	-11%
70	0	0	-1,213	-548	-46	-1,806
	0%	0%	-24%	-15%	-5%	-10%
75	0	0	-608	-741	-97	-1,447
	0%	0%	-12%	-20%	-10%	-8%
80	0	0	0	-837	-148	-985
	0%	0%	0%	-23%	-15%	-6%
85	0	0	0	-336	-195	-532
	0%	0%	0%	-9%	-20%	-3%

Key: HZ – herpes zoster

The incidence and prevalence of PHN disease generated by the model before vaccination corresponded approximately to incidence and prevalence in Ireland estimated using international data. Following the introduction of HZ vaccination, the predicted reduction in PHN cases over the time horizon of the model ranged from 34% when vaccination commenced at 50 years old to 7% when vaccination commenced at 85 years old (Table 6.10). The larger reduction in PHN cases after the introduction of vaccination reflects the protective effect of vaccination against PHN (RR 0.39) included in the model.

Table 6.10 Estimated change in post-herpetic neuralgia (cases and %) by age group and age at vaccination, with 50% coverage, compared with no vaccination

Age group for PHN / Age at vaccination (years)	50-59yr olds	60-69yr olds	70-79yr olds	≥80yr olds	Total
50	-182	-287	-346	-376	-1,191
	-40%	-37%	-32%	-31%	-34%
55	-95	-304	-370	-379	-1,148
	-21%	-39%	-34%	-31%	-32%
60	0	-294	-394	-393	-1,081

Age group for PHN / Age at vaccination (years)	50-59yr olds	60-69yr olds	70-79yr olds	≥80yr olds	Total
	0%	-38%	-37%	-32%	-31%
65	0	-148	-417	-414	-979
	0%	-19%	-39%	-34%	-28%
70	0	0	-396	-439	-834
	0%	0%	-37%	-36%	-24%
75	0	0	-184	-463	-648
	0%	0%	-17%	-38%	-18%
80	0	0	0	-435	-435
	0%	0%	0%	-35%	-12%
85	0	0	0	-234	-234
	0%	0%	0%	-19%	-7%

Key: PHN – post-herpetic neuralgia

6.3.2 Cost-utility analysis

6.3.2.1 Base-case analysis

The ICERs were calculated across 10,000 simulations. Convergence testing indicated that the number of simulations was sufficient to provide a stable result. For all vaccination strategies under consideration, a stable estimate of the ICER was achieved after approximately 3,000 simulations (Appendix C 6.2).

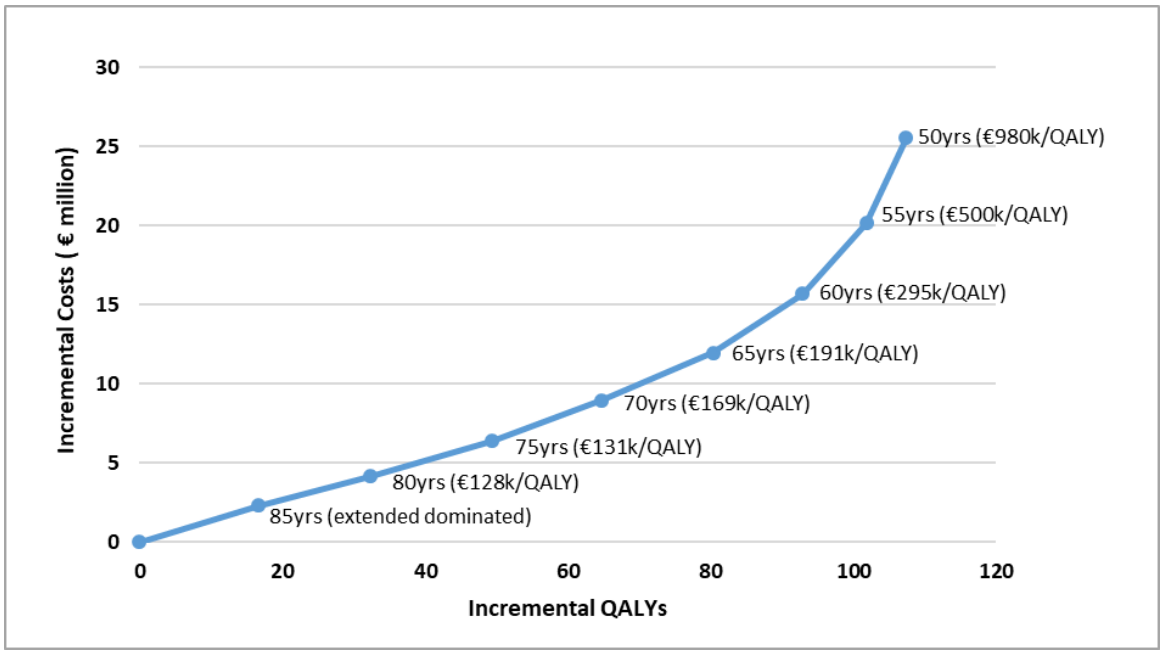
Over the time horizon of the model, and for all vaccination strategies, it was estimated that HZ vaccination would be both more costly and more effective (generate greater QALYs) relative to no vaccination. For all vaccination strategies, the ICERs exceeded €45,000 per QALY and therefore HZ vaccination would not be considered cost effective, at a WTP threshold of €45,000 per QALY gained (Table 6.11). The ICERs were plotted on a cost-effectiveness plane (Figure 6.6) and ranged from €127,824 per QALY with vaccination at 80 years old (compared with no vaccination) to €979,815 per QALY with vaccination at 50 years old (compared with vaccination at 55 years old).

Table 6.11 Results of probabilistic sensitivity analysis (payer perspective)

Age at vaccination (years)*	ACER† (€/QALY)	Incremental costs for ICER (€, million) (95% CI)	Incremental QALYs for ICER (95% CI)	ICER† (€/QALY)
85	139,215	2.3 (1.9 to 2.8)	17 (10 to 28)	139,215 (extended dominated)‡
80	127,824	4.1 (3.4 to 4.9)	32 (18 to 54)	127,824
75	128,996	2.2 (0.9 to 3.6)	17 (6 to 33)	131,222
70	138,561	2.6 (0.6 to 4.6)	15 (1 to 37)	169,150
65	148,720	3.0 (0.4 to 5.7)	16 (-5 to 41)	190,851
60	168,612	3.7 (0.3 to 7.3)	13 (-15 to 45)	295,327
55	197,758	4.5 (0.2 to 8.9)	9 (-25 to 46)	500,344
50	237,754	5.4 (-0.2 to 11.2)	5 (-34 to 28)	979,815

Key: ACER – average cost-effectiveness ratio; QALYs – quality-adjusted life-years
*Ordered from least costly to most costly vaccination strategy.
†ACER compares each vaccination strategy with no vaccination. ICER compares each vaccination strategy with the previous least costly strategy.
‡This strategy is classified as extended dominated as the ICER is greater than a subsequent strategy and it is eliminated from ICER calculations.

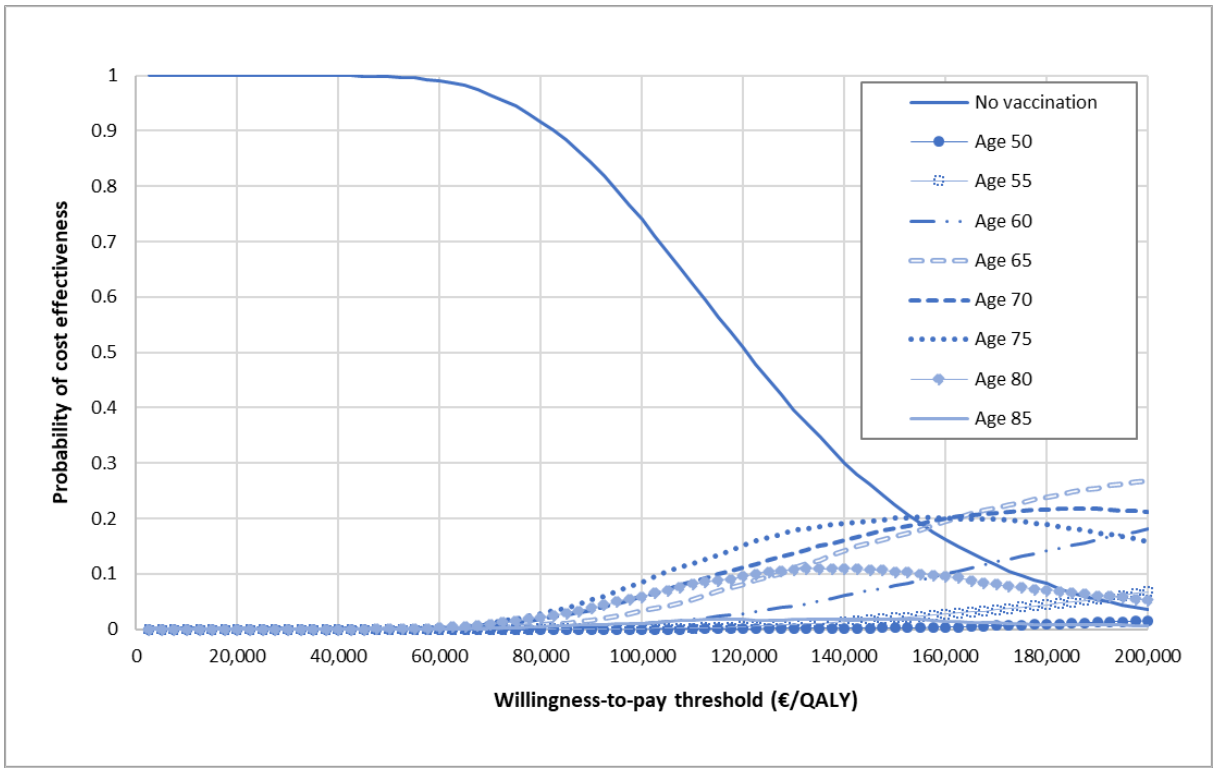
Figure 6.6 Incremental cost-effectiveness plane for herpes zoster vaccination strategies (payer perspective)



Key: QALY – quality-adjusted life-year

The cost-effectiveness acceptability curve (CEAC) summarises the uncertainty in the results of the economic evaluation. It plots the proportion of times that each of the alternative strategies under consideration has the greatest net monetary benefit (that is, the intervention's value in monetary terms) across a range of WTP thresholds. At a WTP threshold of €20,000 per QALY, the probability of any of the HZ vaccination strategies being cost effective was 0%. At a WTP threshold of €45,000 per QALY, the probability of any of the HZ vaccination strategies being cost effective was less than 0.05% (Figure 6.7).

Figure 6.7 Cost-effectiveness acceptability curves for all herpes zoster vaccination strategies



From the societal perspective, which included productivity losses associated with absence from paid work due to HZ illness and primary care costs for those without a medical card or GP visit card, all eight vaccination strategies were both more costly and more effective (generate greater QALYs) relative to no vaccination. For the incremental analysis, where each strategy was compared to the previous least expensive strategy, the ICERs for all strategies exceeded €45,000 per QALY (Table 6.12). Therefore, from the societal perspective, none of the HZ vaccination strategies would be considered cost effective, compared with no vaccination or the previous least expensive strategy, at a WTP threshold of €45,000 per QALY. The ICERs estimated from the payer and societal perspectives did not differ markedly. This is due to lower workforce participation, increasing eligibility for a GP card or medical card and higher risk of HZ as age increases.

Table 6.12 Results of probabilistic sensitivity analysis for societal perspective

Age at vaccination (years)*	ACER† (€/QALY)	Incremental costs for ICER (€, million) (95% CI)	Incremental QALYs for ICER (95% CI)	ICER† (€/QALY)
85	151,394	2.5 (1.4 to 3.5)	16 (-96 to 135)	151,394 (extended dominated)‡
80	127,387	4.1 (2.9 to 5.3)	32 (-74 to 147)	127,387
75	129,087	2.2 (0.6 to 3.8)	17 (-74 to 114)	132,412
70	138,816	2.6 (0.4 to 4.8)	15 (-66 to 101)	169,943
65	150,853	3.1 (0.3 to 6.0)	15 (-58 to 92)	201,024
60	167,707	3.6 (0.001 to 7.2)	13 (-57 to 84)	269,125
55	195,909	4.2 (-0.3 to 9.0)	8 (-57 to 75)	511,730
50	235,300	5.2 (-0.6 to 11.0)	5 (-61 to 135)	987,197

Key: ACER – average cost-effectiveness ratio; QALYs – quality-adjusted life-years

*Ordered from least costly to most costly vaccination strategy.
†ACER compares each vaccination strategy with no vaccination. ICER compares each vaccination strategy with the previous least costly strategy.
‡This strategy is classified as extended dominated as the ICER is greater than a subsequent strategy and it is eliminated from ICER calculations.

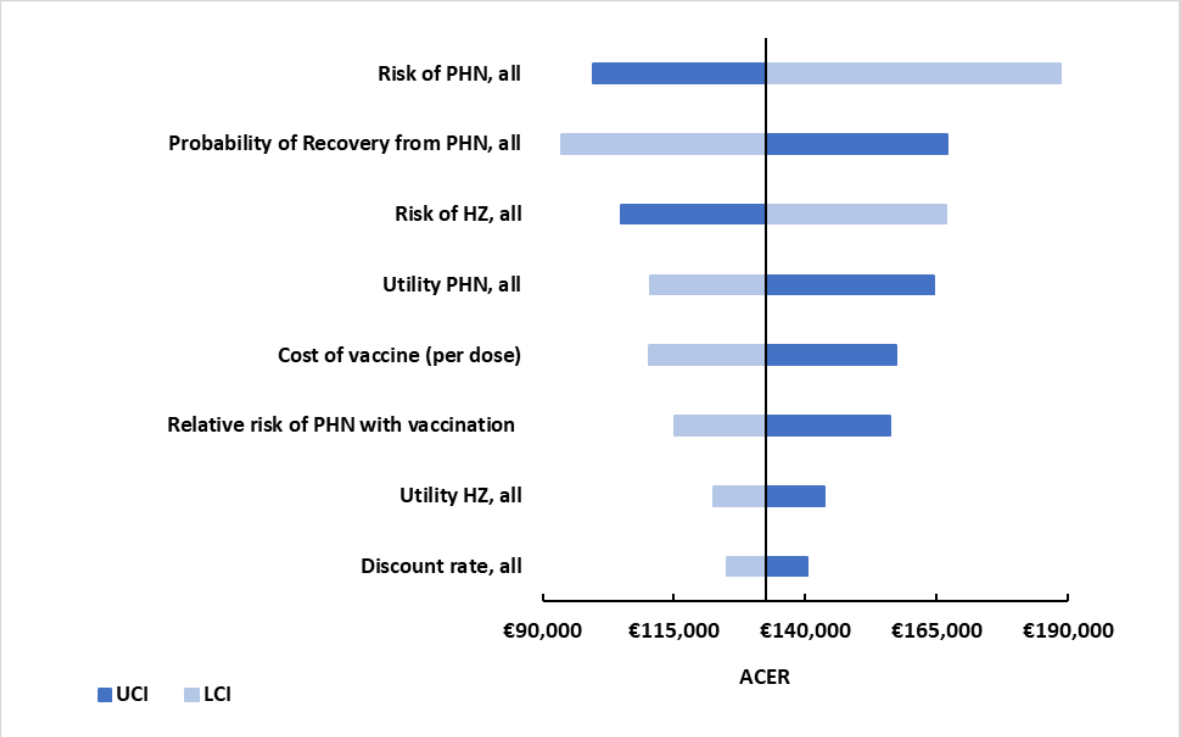
6.3.2.2 Univariate sensitivity analysis

When conducting OWSA, all input parameters are varied individually and ranked in order of increasing influence on the uncertainty in the ICER. To demonstrate the impact of parameter uncertainty, OWSA was conducted from the payer perspective comparing the intervention with the lowest ICER (vaccination at 80 years of age) with no vaccination. OWSA was also conducted to compare vaccination at 65 years of age (representing the mid-point of vaccination strategies) with no vaccination. However, given that the ICER for vaccination at 65 years of age is presented relative

to vaccination at 70 years of age, it should be noted that the OWSA results are presented with respect to the corresponding ACER. Although all parameters were varied in the analysis, only those that result in a ≥10% fluctuation from the mean ICER or ACER are presented (Figure 6.8 and Figure 6.9). None of the OWSA conducted resulted in an ICER or ACER below the WTP threshold of €45,000 per QALY.

The results of the OWSA for vaccination at 80 years of age (compared with no vaccination) were most sensitive to the risk of PHN, the probability of recovery from PHN and the risk of HZ. None of the OWSA resulted in an ACER below €90,000 per QALY (Figure 6.8).

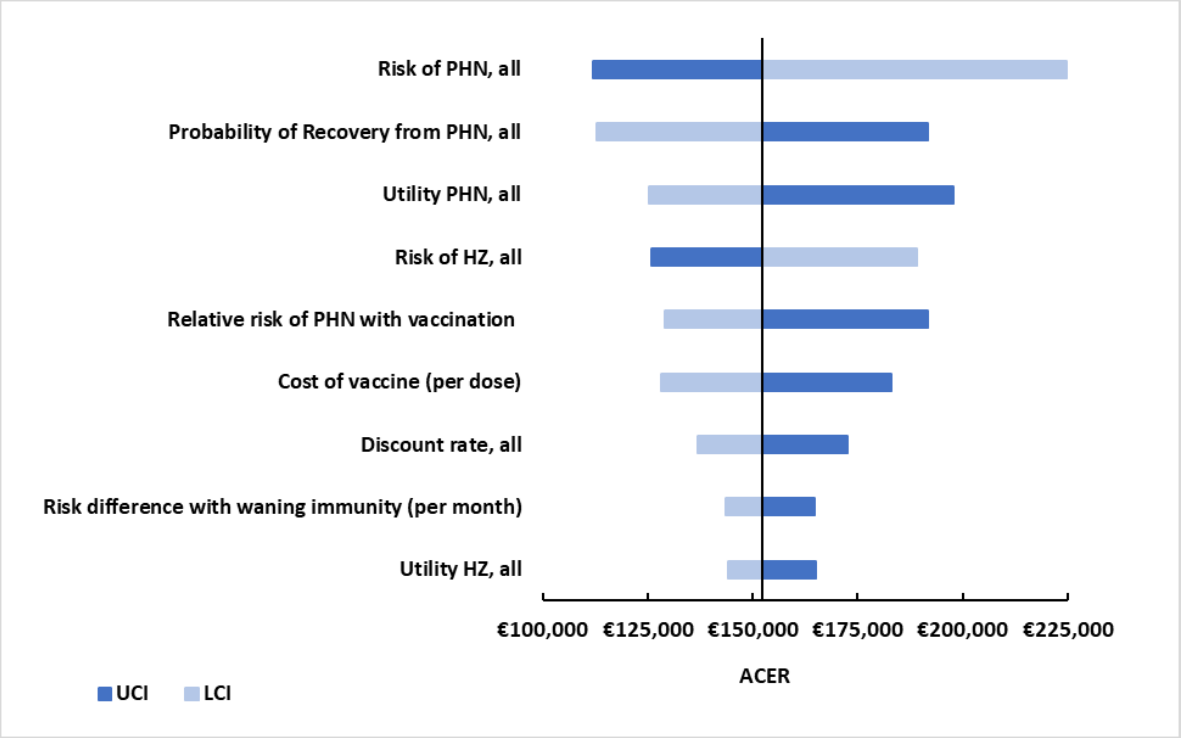
Figure 6.8 Tornado plot of univariate sensitivity analysis for herpes zoster vaccination at 80 years of age versus no vaccination



Key: ICER – incremental cost-effectiveness ratio; HZ – herpes zoster; LCI – lower confidence interval; PHN – post-herpetic neuralgia; UCI – upper confidence interval

The results of the OWSA for vaccination at 65 years of age (versus no vaccination) were most sensitive to the risk of PHN, the probability of recovery from PHN and the utility associated with PHN. None of the OWSA resulted in an ACER below €100,000 per QALY (Figure 6.9).

Figure 6.9 Tornado plot of univariate sensitivity analysis for herpes zoster vaccination at 65 years of age versus no vaccination



Key: ACER – average cost-effectiveness ratio; HZ – herpes zoster; LCI – lower confidence interval; PHN – post-herpetic neuralgia; UCI – upper confidence interval

6.3.2.3 Scenario analysis

Scenario 1

The base-case parameter value for vaccine effectiveness (70.2%) was based on a meta-analysis of RZV effectiveness data from observational studies only (Chapter 4). Based on the observational data, the base-case analysis also included a reduced risk of PHN in those vaccinated but who subsequently develop HZ (risk ratio = 0.386). A scenario analysis was conducted where the parameter value for vaccine effectiveness was based on a meta-analysis of RZV effectiveness data from RCTs only (91.8%). This scenario analysis did not include a reduced risk of PHN in those vaccinated, but who subsequently develop HZ.

For all vaccination strategies assessed, the ICER in this scenario analysis exceeded the ICER from the base-case analysis (Table 6.13).

Table 6.13 Results of scenario analysis of vaccine effectiveness and risk of post-herpetic neuralgia in those vaccinated

Age at vaccination (years)	ICER (€/QALY)
85	158,424 (extended dominated)[†]
80	144,614
75	151,911
70	202,715
65	242,320
60	453,617
55	1,635,242
50	Dominated[‡]

Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life-year

[†]This strategy is classified as 'extended dominated' as the ICER is greater than the subsequent strategy and it is eliminated from ICER calculations.
[‡]This strategy is classified as 'dominated' as the strategy is more costly and less effective than the previous less expensive strategy and it is eliminated from ICER calculations.

Across all vaccination strategies, the percentage reduction in HZ cases with vaccination was greater in the scenario analysis than the base-case analysis, while the percentage reduction in PHN cases with vaccination was greater in the base-case analysis (Table 6.14).

Table 6.14 Estimated total reduction (%) in herpes zoster and post-herpetic neuralgia cases with vaccination, for scenario analysis using randomised controlled trial vaccine effectiveness data

Age at vaccination (years)	Base-case analysis (observational data)		Scenario analysis (RCT data)	
	HZ	PHN	HZ	PHN
50	-20%	-67%	-37%	-31%
55	-22%	-65%	-39%	-36%
60	-23%	-61%	-39%	-39%
65	-23%	-55%	-36%	-39%
70	-21%	-47%	-31%	-35%
75	-17%	-37%	-24%	-29%
80	-11%	-25%	-16%	-20%
85	-6%	-13%	-8%	-11%

Key: HZ – herpes zoster; PHN – post-herpetic neuralgia; RCT – randomised controlled trial

Scenario 2

In the base case scenario, it was assumed that the cost of administration of the HZ vaccine for all individuals would be borne by the health and social care system. A scenario analysis was conducted where it was assumed that the health and social care system would cover the vaccine administration fee for those with a medical card or GP visit card only. In all vaccination strategies assessed, the ICER exceeded the WTP threshold of €45,000 per QALY (Table 6.15).

Table 6.15 Results of scenario analysis with vaccine administration cost included for only those with a medical card or GP visit card

Age at vaccination (years)	ICER (€/QALY)
85	144,440 (extended dominated)†
80	132,612
75	136,821
70	170,080 (extended dominated)†
65	153,807
60	266,573
55	489,743
50	954,191

Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life-year

†This strategy is classified as 'extended dominated' as the ICER is greater than a subsequent strategy and it is eliminated from ICER calculations.

Scenario 3:

In the base-case analysis conducted from the societal perspective, productivity loss due to absence from paid work was limited to those with HZ only. In addition to including productivity loss for those with HZ, a scenario analysis was conducted that also included productivity loss associated with absence from paid work for those with PHN. It was assumed that the average absence from paid work for those with PHN was 22 working days. In all vaccination strategies assessed, the ICER exceeded the WTP threshold of €45,000 per QALY (Table 6.16).

Table 6.16 Results of scenario analysis with inclusion of productivity losses associated with post-herpetic neuralgia

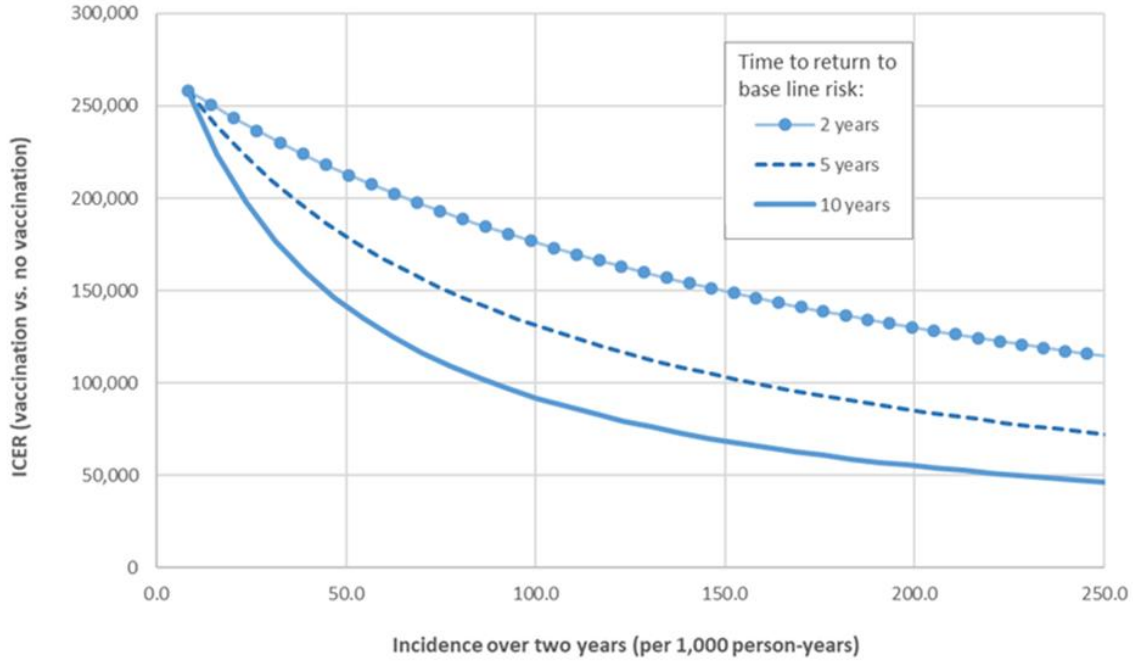
Age at vaccination (years)*	ACER† (€/QALY)	ICER† (€/QALY)
85	140,898	140,898 (extended dominated)‡
80	117,143	117,143 (extended dominated)‡
75	116,441	116,441
70	124,510	150,391
65	135,689	181,880
60	153,600	267,300
55	179,841	459,935
50	218,111	972,940

Key: ACER – average cost-effectiveness ratio; ICER – incremental cost-effectiveness ratio; QALYs – quality-adjusted life-years
*Ordered from least costly to most costly vaccination strategy.
†ACER compares each vaccination strategy with no vaccination. ICER compares each vaccination strategy with the previous least costly strategy.
‡This strategy is classified as extended dominated as the ICER is greater than a subsequent strategy and it is eliminated from ICER calculations.

Scenario 4

Given that a CUA was not conducted for the immunocompromised cohort, a scenario analysis was conduct to explore the impact of an increased risk of HZ on the cost effectiveness of vaccination. The increased risk of HZ was varied across a wide range of values and for different durations of elevated risk. At the most extreme values, where it was assumed that it would take 10 years for elevated risk to return to general population levels, HZ vaccination at 50 years of age was not cost effective at incidence of up to 250 cases per 1,000 person-years (Figure 6.10). Such an incidence implies a relative risk of approximately 31, which is well in excess of the incidence of HZ reported for individuals that have undergone HCST or solid organ transplant, or are living with HIV.[106, 318]

Figure 6.10 Incremental cost effectiveness of herpes zoster vaccination at age 50 years, by incidence of herpes zoster and duration of increased risk of herpes zoster



Key: ICER – incremental cost-effectiveness ratio

6.3.2.4 Threshold analysis

A deterministic threshold analysis was conducted to assess the impact of a lower vaccine price (beyond the reduction used in the OWSA) on the cost effectiveness of HZ vaccination. All other parameters were held at their mean value during the analysis.

When the vaccine price (per dose) was set at both €100.00 and €50.00, the ICERs for all vaccination strategies remained above the WTP threshold of €45,000 per QALY. At a price of €30.00 per vaccine dose, the ICERs for all vaccination strategies remained above the WTP threshold of €45,000 per QALY with the exception of vaccination at 75 and 80 years of age (Table 6.17).

Table 6.17 Threshold analysis of vaccine price (per dose) on incremental cost-effectiveness ratio (€/QALY)

Age at vaccination (years)	ICER (€/QALY) Vaccine price = €100 (per dose)	ICER (€/QALY) Vaccine price = €50 (per dose)	ICER (€/QALY) Vaccine price = €30 (per dose)
85	101,704 (extended dominated)†	59,806 (extended dominated)†	43,047 (extended dominated)†
80	92,967	54,100	38,553
75	96,099	56,175	40,205
70	124,348	73,003	52,465
65	135,531	76,342	52,667
60	216,634	129,768	95,021
55	383,599	232,480	172,536
50	770,459	463,534	340,764

Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life-year

†This strategy is classified as extended dominated as the ICER is greater than a subsequent strategy and it is eliminated from ICER calculations.

6.3.3 Budget-impact analysis – general population aged 50 years and older

For the purposes of the BIA for the general population aged 50 years and older, the estimated annual eligible number of people for vaccination for each age cohort was calculated based on the current population and adjusted for the number of persons with immunocompromising conditions (Chapter 3 and Table 6.18). The adjustment (by age group) was estimated by calculating the proportion of immunocompromised persons in the total population using the COVAX data.[175]

Table 6.18 Estimated annual number of eligible adults in the general population aged 50 years and older for herpes zoster vaccination

Age at vaccination (years)	Total population	Percentage immunocompromised†	General population not immunocompromised
50	72,249	4.0%	69,333
55	62,916	4.0%	60,377
60	57,518	5.9%	54,149
65	50,083	5.9%	47,150
70	43,150	7.3%	40,020
75	35,767	7.3%	33,173
80	22,847	6.9%	21,275
85	14,457	6.9%	13,462

†Calculated based on the total number of immunocompromised people registered in the COVAX system as a proportion of the total population.

The BIA for each of the vaccination strategies is presented relative to no vaccination. The budget impact is limited to the vaccination programme costs (including vaccine procurement, vaccine administration, national cold chain service, and education and communication), and the costs averted as a result of a decrease in incidence of disease associated with the introduction of a vaccination programme. In line with national guidelines,[272] VAT is included in the BIA. VAT on non-oral drugs (such as injectables) is standard rated[319] (23% as of February 2024[320]), while services delivered by a recognised medical professional for the purpose of protecting health (for example, vaccine administration) are VAT exempt.[321] Potential organisational issues associated with the introduction of an HZ vaccination programme are described in Chapter 8.

6.3.3.1 Base-case analysis

Assuming a vaccine price of €151.00 + VAT per dose and 50% coverage, the five-year incremental budget impact ranged from €76.8 million for vaccination at 50 years old to €15.2 million for vaccination at 85 years old. The five-year incremental budget impact for each of the vaccination strategies is presented in Table 6.19. The majority of costs incurred (approximately 94%) over the five-year time horizon related to vaccine procurement (83%) and administration (11%). For each vaccination strategy, the total cost offsets were less than 1% of the total costs

incurred as a result of vaccination over the five-year period. The largest cost offsets related to hospitalisation and ranged from €24,304 when vaccination commenced at 50 years of age to €61,884 when vaccination commenced at 85 years of age.

Table 6.19 Results of base-case analysis for five-year budget impact analysis for adults in the general population aged 50 years and older

Age at HZ vaccination (years)	Total eligible population	Vaccinated population (50% coverage)	Costs incurred (€ million)	Costs averted (€ million)	5-year incremental budget impact (€ million)
50	69,333	34,667	76.89	0.05	76.84
55	60,377	30,188	67.01	0.06	66.95
60	54,149	27,598	61.26	0.08	61.18
65	47,150	24,031	53.41	0.10	53.31
70	40,020	20,311	45.51	0.16	45.35
75	33,173	16,836	37.77	0.17	37.60
80	21,275	10,754	24.13	0.17	23.96
85	13,462	6,805	15.27	0.12	15.15

Key: HZ – herpes zoster

6.3.3.2 Univariate sensitivity analysis

As in the CUA, univariate sensitivity analysis was undertaken to assess the impact of variations in input parameters on the five-year budget impact of introducing an HZ vaccination programme. Uncertainty relating to the coverage rate and the cost of the vaccine was found to contribute most to the budget impact of all vaccination strategies. At 30% coverage, the five-year incremental budget impact ranged from €46.1 million for vaccination at 50 years old to €9.1 million for vaccination at 85 years old. At 70% coverage, the five-year incremental budget impact ranged from €107.6 million for vaccination at 50 years old to €21.2 million for vaccination at 85 years old. Given that there is no capital investment required for the implementation of an HZ vaccination programme, the budget impact of changes in the coverage rate reflect the corresponding increase or decrease in the coverage rate. The five-year incremental budget impact for all vaccination strategies with varying coverage rates is presented in Table 6.20.

Table 6.20 Results of one-way sensitivity analysis of coverage rate for five-year budget impact analysis for adults in the general population aged 50 years and older

Age at HZ vaccination (years)	50% coverage		30% coverage		70% coverage	
	Vaccinated population	5-year incremental budget impact, € million	Vaccinated population	5-year incremental budget impact, € million	Vaccinated population	5-year incremental budget impact, € million
50	34,667	76.8	20,800	46.1	48,533	107.6
55	30,188	66.9	18,113	40.2	42,264	93.7
60	27,598	61.2	16,559	36.7	38,638	85.7
65	24,031	53.3	14,419	32.0	33,643	74.6
70	20,311	45.4	12,187	27.2	28,436	63.5
75	16,836	37.6	10,102	22.6	23,570	52.6
80	10,754	24.0	6,453	14.4	15,056	33.5
85	6,805	15.1	4,083	9.1	9,527	21.2

Key: HZ – herpes zoster

In the base-case scenario, it was assumed that the vaccine price was €151.00 + VAT per dose. In the OWSA, the price per vaccine dose was varied by +/-20%. The incremental budget impact with varying vaccine prices is presented in Table 6.21. At a price of €121 + VAT per vaccine dose (and 50% coverage), the incremental budget impact ranged from €63.4 million with vaccination at 50 years old to €12.5 million with vaccination at 85 years old. This represented a reduction of 18% (compared with the base case) in the total budget impact for each of the vaccination strategies. At a price of €181 + VAT per vaccine dose (and 50% coverage), the incremental budget impact ranged from €90.3 million with vaccination at 50 years old to €17.8 million with vaccination at 85 years old. This represented an increase of 18% (compared with the base case) in the total budget impact for each of the vaccination strategies.

6.3.3.3 Scenario analysis

Scenario 1

In the BIA it was estimated that the cost of vaccine procurement comprises approximately 84% of the total vaccination programme costs for all vaccination strategies. However, as highlighted in the CUA, there is uncertainty with regard to the cost of the vaccine. Therefore, in addition to the univariate sensitivity analysis above, the cost of the vaccine was set at both €100 + VAT per dose and €50 + VAT per dose. At a price of €100 + VAT per vaccine dose (and 50% coverage), the incremental budget impact ranged from €53.9 million with vaccination at 50 years old to €10.6 million with vaccination at 85 years old. This represented a reduction of 30% (compared with the base case) in the total budget impact for each of the vaccination strategies. At a price of €50 + VAT per vaccine dose (and 50% coverage), the incremental budget impact ranged from €31.4 million with vaccination at 50 years old to €6.2 million with vaccination at 85 years old. This represented a reduction of 59% (compared with the base case) in the total budget impact for each of the vaccination strategies (Table 6.21).

Scenario 2

The base-case analysis was conducted based on eligibility for HZ vaccination at specified ages from 50 to 85 years old inclusive. Two scenario analyses were conducted to estimate the potential budget impact of offering HZ vaccination to all adults aged 65 years and older and all adults aged 85 years and older.

If HZ vaccination was offered to all adults aged 65 years and older, it was assumed that the initial eligible cohort in year one would be approximately 776,000 people and the eligible cohort in each of years two to five inclusive would be approximately 48,000. Based on a vaccine price of €151.00 + VAT per dose, a vaccine administration of €25 per dose and a coverage rate of 50%, the incremental five-year budget impact was estimated at €218 million, comprising €222 million in incremental costs and €4.2 million in costs averted. The incremental budget impact was estimated at €172.8 million in year one and €11.3 million per annum in years two to five.

If HZ vaccination was offered to all adults aged 85 years and older, it was assumed that the initial eligible cohort in year one would be approximately 84,500 people and the eligible cohort in each of years two to five inclusive would be approximately 19,000. Based on a vaccine price of €151.00 + VAT per dose, a vaccine administration of €25 per dose and a coverage rate of 50%, the incremental budget impact was estimated at €35 million, comprising €36.3 million in incremental costs and €1.3 million in costs averted. The incremental budget impact was estimated at

€18.8 million in year one and €4.1 million per annum per annum in years two to five. For both scenarios, vaccine procurement and administration comprised 94% of the incremental costs.

Table 6.21 Results of one-way sensitivity analysis and scenario analysis of vaccine price for five-year budget impact analysis for adults in the general population aged 50 years and older

Age at HZ vaccination (years)	Vaccinated population (50% coverage)	Vaccine price €151 + VAT per dose*	Vaccine price €181 + VAT per dose	Vaccine price €121 + VAT per dose	Vaccine price €100 + VAT per dose	Vaccine price €50 + VAT per dose
		5-year incremental budget impact, € million				
50	34,667	76.8	90.3	63.4	53.9	31.4
55	30,188	66.9	78.7	55.2	47.0	27.4
60	27,598	61.2	71.9	50.4	42.9	25.0
65	24,031	53.3	62.7	44.0	37.4	21.8
70	20,311	45.4	53.3	37.5	31.9	18.8
75	16,836	37.6	44.1	31.0	26.5	15.6
80	10,754	24.0	28.1	19.8	16.8	9.9
85	6,805	15.1	17.8	12.5	10.6	6.2

Key: HZ – herpes zoster; VAT – value-added tax

*Base-case analysis

6.3.4 Budget-impact analysis – immunocompromised persons

For the BIA for immunocompromised persons, the sources for potential eligible numbers of people for vaccination are described in detail in Chapter 3. In year one of the BIA, the number of persons assumed eligible for HZ vaccination included the:

- total number of persons with non-specific immunocompromising conditions aged 50 years and over registered in the COVAX system
- estimated total number of persons aged 18 to 49 years with advanced or untreated HIV
- average annual number of HSCT recipients aged 18 years and over (2017 to 2021) plus 100% of individuals aged 18 years and over who had undergone HSCT in the previous five years; included also were CAR T-cell therapy recipients aged 18 years and over assuming an average annual of 50 patients per year and 100% of individuals who had undergone this treatment since the service was initiated in 2021. [165]
- average annual number of solid organ transplant recipients aged 18 to 49 years (2016 to 2021, excluding 2020) plus the prevalent population of solid organ transplant recipients aged 18 to 49 years
- average annual number of persons aged 18 to 49 years with haematological malignancies (2015 to 2019) plus the prevalent population of persons aged 18 to 49 years.

For each of years two to five of the BIA, the number of persons aged 50 years and over with non-specific immunocompromising conditions was assumed to be equal to the estimated total number of annual deaths (using all-cause mortality rates) in this cohort. That is, it was assumed that the number that die within the cohort in a year would be replaced with an equal number of new persons with non-specific immunocompromising conditions who would themselves become eligible for HZ vaccination. For those with advanced or untreated HIV, it was assumed that the number of persons with a late first diagnosis of HIV in 2022 would apply for each of years two to five of the BIA. For HSCT recipients, the eligible prevalent population in year one was assumed to include up to 100% of individuals that had undergone HSCT in the previous five years.[322] For solid organ transplants, it was assumed that all surviving transplant recipients would form the prevalent population in year one, in addition to new recipients in that year. The population size was approximated using data on survival and historical numbers of transplants.[167-170, 323] In relation to individuals being treated for haematological malignancies, it was assumed that the prevalent population would include cases treated up to 12 months prior to the start

of the vaccination programme. The estimated total number of immunocompromised persons eligible for HZ vaccination and included in the BIA are provided in Table 6.22.

Table 6.22 Estimated number of immunocompromised persons eligible for herpes zoster vaccination by year*

	Non-specific IC conditions	HSCT recipients	Solid organ transplant recipients	Haematological malignancies	Advanced / untreated HIV	Total persons
Year 1	94,398	1,588	3,769	4,666	1,100	105,521
Year 2	2,222	298	269	2,333	78	5,200
Year 3	2,222	298	269	2,333	78	5,200
Year 4	2,222	298	269	2,333	78	5,200
Year 5	2,222	298	269	2,333	78	5,200

Key: HIV – human immunodeficiency virus; HSCT – haematopoietic stem cell transplantation; IC – immunocompromising
*Sources: Immunocompromising conditions,[173, 175] HSCT recipients,[159-164] solid organ transplant recipients,[167-170] haematological malignancies,[171] advanced/untreated HIV.[173, 174]

The BIA is presented relative to no vaccination. The budget impact is limited to the vaccination programme costs (including vaccine procurement, vaccine administration, national cold chain service, and education and communication). Given the uncertainty about the age of and risk of HZ and PHN in this cohort, the potential costs averted as a result of a decrease in incidence of disease associated with the introduction of a vaccination programme for immunocompromised persons have not been included in the BIA, with one exception relating to the BIA for HSCT recipients. Cost-offsets relating to the reduction in prescribing of valaciclovir for VZV prophylaxis for HSCT recipients following vaccination have been included in the BIA. Based on expert advice, it was assumed that the proportion of HSCT recipients taking VZV prophylaxis would reduce by 50% in the year following vaccination, with a further decrease of 10% each year thereafter. Adopting a conservative approach, it was assumed that the HSE would accrue cost savings relating to valaciclovir for those with medical cards only. Based on current medical card eligibility data for the general population, it was assumed that 24.7% (estimated as a weighted average based on general population eligibility for a medical card for those aged 18 to 69 years) of HSCT recipients would have a medical card.[305]

6.3.4.1 Base-case analysis

Assuming a vaccine price of €151.00 + VAT per dose and 100% coverage for eligible immunocompromised persons, the five-year incremental budget impact was estimated at €56.18 million. The five-year incremental budget impact for each of the immunocompromised cohorts (Table 6.23) ranged from €46.3 million for the cohort with non-specific immunocompromising conditions to €0.6 million for the cohort with advanced/untreated HIV. As noted, with the exception of offsets due to reduction in prescribing of VZV prophylaxis for HSCT recipients, these figures do not include potential cost offsets associated with cases or hospitalisations avoided. For all cohorts, the incremental budget impact in year one was significantly greater than years two to five as it was assumed that all those currently eligible for vaccination would be vaccinated in year one. Beyond year one, it was assumed that only additions to these cohorts would be vaccinated. As with the BIA for adults in the general population aged 50 years and older, the majority (approximately 94%) of costs incurred over the five-year time horizon related to vaccine procurement (83%) and administration (11%).

Table 6.23 Results of base-case analysis (100% coverage) for five-year budget-impact analysis for immunocompromised persons

Year of BIA	Non-specific IC conditions	HSCT recipients	Solid organ transplant recipients	Haematological malignancies	Advanced/ untreated HIV	Total budget impact, € million
Year 1	42.36	0.72	1.69	2.09	0.49	47.35
Year 2	1.00	0.06	0.12	1.05	0.03	2.26
Year 3	1.00	0.03	0.12	1.05	0.03	2.26
Year 4	1.00	-0.01	0.12	1.05	0.03	2.19
Year 5	1.00	-0.04	0.12	1.05	0.03	2.16
Total	**46.34**	**0.74**	**2.17**	**6.28**	**0.63**	**56.18**

Key: HIV – human immunodeficiency virus; HSCT – haematopoietic stem cell transplantation; IC – immunocompromising

6.3.4.2 Univariate sensitivity analysis

As in the BIA for adults in the general population aged 50 years and over, univariate sensitivity analysis was undertaken to assess the impact of variations in input parameters on the five-year budget impact of introducing an HZ vaccination programme. At 50% coverage, the estimated five-year incremental budget impact for immunocompromised persons was €28.1 million (Table 6.24).

Table 6.24 Results of one-way sensitivity analysis of coverage rate (50%) for five-year budget impact analysis (€, million) for immunocompromised persons

Year of BIA	Non-specific IC conditions	HSCT recipients	Solid organ transplant recipients	Haematological malignancies	Advanced/ untreated HIV	Total budget impact, € million
Year 1	21.18	0.36	0.85	1.05	0.25	23.67
Year 2	0.50	0.03	0.06	0.52	0.17	1.13
Year 3	0.50	0.01	0.06	0.52	0.17	1.11
Year 4	0.50	0.00	0.06	0.52	0.17	1.10
Year 5	0.50	-0.02	0.06	0.52	0.17	1.08
Total	**23.17**	**0.37**	**1.09**	**3.14**	**0.32**	**28.09**

Key: BIA – budget-impact analysis; HIV – human immunodeficiency virus; HSCT – haematopoietic stem cell transplantation; IC – immunocompromising

In the base-case scenario, it was assumed that the vaccine price was €151.00 + VAT per dose. In the OWSA, the price per vaccine dose was varied by +/-20%. The incremental budget impact with varying vaccine prices is presented in Table 6.25. At a price of €121 + VAT per vaccine dose, the five-year incremental budget impact was €46.4 million, and at a price of €181 + VAT per dose, the incremental budget impact was €66.0 million.

Table 6.25 Results of one-way sensitivity analysis of vaccine price for five-year budget impact analysis (€, million) for immunocompromised persons

Vaccine price (€) per dose	Non-specific IC condition	HSCT recipients	Solid organ transplant recipients	Haematological malignancies	Advanced/ untreated HIV	Total budget impact, € million
151+VAT[†]	46.34	0.74	2.17	6.28	0.63	56.18
121+VAT	38.31	0.53	1.80	5.19	0.52	46.35
181+VAT	54.38	0.96	2.55	7.37	0.74	66.00

Key: HIV – human immunodeficiency virus; HSCT – haematopoietic stem cell transplantation; IC – immunocompromising; VAT – value-added tax
[†]Base-case analysis

6.3.4.3 Scenario analysis

Scenario 1

In the BIA it was estimated that the cost of vaccine procurement comprises approximately 83% of the total vaccination programme costs for all vaccination strategies. However, as highlighted in the CUA, there is uncertainty with regard to the cost of the vaccine. Therefore, in addition to the univariate sensitivity analysis above, the cost of the vaccine was set at both €100 + VAT and €50 + VAT per dose. At a price of €100 + VAT per vaccine dose (and 100% coverage), the incremental budget impact was €39.5 million, and at a price of €50 + VAT per vaccine dose, the incremental budget impact was €23.1 million (Table 6.26).

Table 6.26 Results of scenario analysis of vaccine price for five-year budget impact analysis (€, million) for immunocompromised persons

Vaccine price (€) per dose	None-specific IC condition	HSCT recipients	Solid organ transplant recipients	Haematological malignancies	Advanced/ untreated HIV	Total budget impact, € million
151+VAT[†]	46.34	0.74	2.17	6.28	0.63	56.18
100+VAT	32.69	0.38	1.53	4.43	0.45	39.47
50+VAT	19.30	0.01	0.91	2.62	0.26	23.09

Key: HIV – human immunodeficiency virus; HSCT – haematopoietic stem cell transplantation; IC – immunocompromising; VAT – value-added tax
[†]Base-case analysis

Scenario 2

In the base-case analysis, it was assumed that 94,398 individuals aged 50 years and over with non-specific immunocompromising conditions were eligible for HZ vaccination. Given the uncertainty around this parameter value, a scenario analysis was conducted. The value was adjusted to align with data from the HPSC reporting that 137,188 persons aged 50 years and over with a medical risk condition availed of influenza vaccination in the 2022-2023 season.(176) Assuming that 137,188 persons with non-specific immunocompromising conditions are eligible for HZ vaccination and 100% coverage, the total five-year incremental budget impact for those with immunocompromising conditions increased by 37%, from €56.2 million in the base-case scenario to €77.2 million.

6.4 Discussion

A de novo economic model was developed to assess the impact of the introduction of HZ vaccination for adults in Ireland. The model assessed the introduction of vaccination at eight different ages for adults in the general population aged 50 years and older and was used to estimate the cost effectiveness and budget impact of the introduction of HZ vaccination for adults in Ireland. A separate BIA was conducted to assess the budget impact of HZ vaccination for identified subgroups of immunocompromised persons. The analysis of cost effectiveness was conducted from both the payer (HSE) and societal perspectives, while the BIAs estimated the incremental cost to the HSE of implementing a vaccination programme over a five-year time horizon.

6.4.1 Main findings

Results from the epidemiological analysis indicate that overall incidence of HZ disease is expected to fall after the introduction of HZ vaccination for adults. Following the introduction of HZ vaccination with a 50% coverage rate, the estimated cumulative reduction in HZ cases in the 10 years following vaccination ranges from a total of 494 cases with vaccination at 85 years old to 1,213 cases with vaccination at both 65 and 70 years old. The estimated cumulative reduction in PHN cases in the 10 years following vaccination ranges from a total of 130 cases with vaccination at 50 years old to 264 cases with vaccination at 70 years old.

In terms of cost effectiveness from the payer perspective, none of the vaccination strategies were estimated to be cost effective, relative to no vaccination, or the previous least costly strategy at a WTP threshold of €45,000 per QALY. The probabilistic ICERs ranged from €127,824 per QALY with vaccination at 80 years old to €979,815 per QALY with vaccination at 50 years old. Additionally, none of the OWSA conducted resulted in an ICER or ACER below the WTP threshold of €45,000 per QALY. Similarly, from the societal perspective, none of the vaccination strategies were estimated to be cost effective, relative to no vaccination or the previous least costly strategy, at a WTP threshold of €45,000 per QALY. The ICERs from the societal perspective ranged from €127,387 with vaccination at 80 years old to €987,197 with vaccination at 50 years old. When evaluating population vaccination programmes, a societal perspective captures benefits of vaccination including productivity gains where vaccination prevents disease and resulting absence from work due to illness. However, due to increasing risk of HZ with increasing age but lower workforce participation with increasing age, the productivity gains are not substantial in the case of HZ vaccination.

A scenario analysis was conducted to explore the impact of an increased risk of HZ on the cost effectiveness of vaccination and used specifically to consider

immunocompromised populations. At the levels of HZ incidence reported for individuals who have undergone solid organ transplant or HSCT or are living with HIV, it was found that vaccination at age 50 years would not be cost effective at a WTP threshold of €45,000 per QALY. It is important to note, however, that other than incidence of HZ and vaccine effectiveness, the model parameters were unchanged from the base-case analysis. Immunocompromised individuals may be at higher risk of complications or severe disease relative to the general population. In addition, developing HZ may complicate treatment and the clinical management of those individuals in ways that were not captured in the model.

Given the high degree of uncertainty relating to the cost of the vaccine, a threshold analysis was conducted to determine what the vaccine price would need to be for the ICERs to fall at or below the WTP threshold of €45,000 per QALY. The analysis demonstrated that the vaccine price (per dose) would need to fall by approximately 80% (from €151.00 used in the base case analysis to €30.00) before the ICERs for those vaccinated at 75 or at 80 years of age falls below the WTP threshold of €45,000 per QALY. However, at a price of €30.00 per dose, the ICERs for those vaccinated at 50, 55, 60, 65 or 70 years of age remained above the WTP threshold of €45,000 per QALY.

In the base-case analysis (with 50% coverage), the five-year incremental budget impact of an HZ vaccination programme for adults in the general population aged 50 years and older ranged from €15.1 million with vaccination at 85 years old to €76.8 million with vaccination at 50 years old. The cost of vaccine procurement and administration comprised the majority (94%) of the budget impact associated with the introduction of an HZ vaccination programme. The predicted reduction in HZ cases and the associated fall in the number of hospitalised cases contributed to limited cost savings. For each vaccination strategy, the total cost offsets were less than 1% of the total costs incurred as a result of vaccination over the five-year period. In the OWSA, when the vaccine price was set at the lower estimate of €121 + VAT (per dose), it was estimated that the budget impact would be €12.5 million with vaccination at 85 years old, rising to €63.4 million with vaccination at 50 years old.

In the base-case analysis (with 100% coverage), the five-year incremental budget for eligible immunocompromised persons was estimated at €56.2 million. Due to the uncertainty about the age of and risk of HZ and PHN in this cohort, with the exception of offsets due to a reduction in prescribing of valaciclovir for VZV prophylaxis for HSCT recipients following vaccination, the five-year incremental budget impact does not include the potential cost offsets associated with a reduction in cases, and or hospitalisations avoided. However, given the overall low rate of hospitalisation for HZ, this would not significantly impact the results of the BIA. As

with the BIA for adults in the general population aged 50 years and older, the majority (approximately 94%) of costs incurred over the five-year time horizon related to vaccine procurement (83%) and administration (11%). The estimate of €56.2 million comprised €46.3 million for the cohort with non-specific immunocompromising conditions, €6.3 million for those with haematological malignancies, €2.2 million for solid organ transplant recipients, €745,000 for HSCT recipients and approximately €630,000 for the cohort with advanced/untreated HIV. For all cohorts, the incremental budget impact in year one was significantly greater than years two to five as it was assumed that all those currently eligible for vaccination would be vaccinated in year one. Beyond year one, it was assumed that only additions to these cohorts would be vaccinated and therefore, from years two to five, the total annual incremental budget impact for eligible immunocompromised persons was estimated at between €2.2 million and €2.3 million. The cohorts with haematological malignancies and non-specific immunocompromising conditions accounted for approximately 45% (€1.05 million) and 43% (€1.0 million), respectively, of the annual budget impact from year two to five, inclusive. There is a high degree of uncertainty relating to the number of persons with non-specific immunocompromising conditions who may be eligible for HZ vaccination. The scenario analysis highlighted that the estimated total incremental five-year budget impact of HZ vaccination for those with immunocompromising conditions could potentially rise to €77.2 million, depending on the number of persons with non-specific immunocompromising conditions.

6.4.2 Limitations

As with any economic modelling exercise, the certainty of the results is limited by the underlying assumptions that underpin the model structure, the availability of data to populate the model and the chosen parameter values.

The incidence of both HZ and PHN in Ireland are uncertain. While sentinel surveillance data for HZ are available, these data likely underestimate the true incidence of disease as not all of those with HZ may seek medical care. Incidence of both HZ and PHN were therefore estimated using international data, with calculated estimates higher than those reported from the sentinel data. While higher incidence data biases in favour of vaccination, when the rates were set at the higher values in the OWSA, none of the vaccination strategies were cost effective at a WTP threshold of €45,000 per QALY.

Owing to limitations in the evidence base for Ireland, the only specific complication of HZ that was included as a separate health state in the economic model was PHN. However, in estimating the costs and outcomes associated with HZ, the hospitalisation data specifically included discharges with a primary diagnosis of HZ

and with DRG codes including those with nervous system infection, acute and major eye infection and major skin disorders.

Evidence from the systematic review of clinical effectiveness and safety highlighted considerable differences in vaccine effectiveness between data from RCTs and observational studies. Given the uncertainty in vaccine effectiveness, a conservative approach was adopted where the vaccine effectiveness data from the observational studies were used in the base-case analysis and RCT data were used in a scenario analysis. The results of the CUA did not change in the scenario analysis with none of the vaccination strategies cost effective at a WTP threshold of €45,000 per QALY. The available RCT evidence suggested a decrease in vaccine effectiveness over time of 25% over 10 years, which was incorporated into the model.

The cost of vaccines to the HSE are part of confidential pricing agreements with the vaccine manufacturers and typically these negotiations commence at the beginning of the procurement process following a decision regarding the eligible cohort for whom the vaccine will be funded. Therefore, for the purpose of this HTA, and in the absence of an indicated HZ vaccine price, a cost of €151.00 (excluding VAT) per vaccine dose was assumed in the economic analysis. This was based on the vaccine price used in the studies assessed in the rapid review of modelling studies (Chapter 5), and the advertised cost for private vaccination in Ireland. The sensitivity analysis conducted for both the CUA and BIA highlight the considerable impact of the uncertainty associated with the vaccine cost. The five-year budget impact was particularly sensitive to changes in the vaccine cost. However, when the vaccine cost was set at the lower value (€121 excluding VAT per dose) in the OWSA for the CUA, the ICERs remained above the WTP threshold of €45,000 per QALY. The threshold analysis, where the vaccine price was lowered considerably (to €30 per dose), demonstrated how far the vaccine price would have to fall for the ICERs to fall below €45,000 per QALY. Given that there is currently only a single recombinant vaccine for HZ available, the potential to negotiate substantial price reductions, as part of a competitive tender, may be limited.

There are a number of challenges with respect to the estimation of health-state utility values and the generation of QALYs, leading to considerable uncertainty with respect to utility values used in the model. The review of original studies that elicited health-state utility values or disutilities for HZ and PHN disease states identified substantial heterogeneity across studies. Utility was frequently measured at different time points and some studies reported long-term utility values without disaggregating into HZ and PHN. Additionally, studies that reported utility values for PHN often involved smaller sample sizes with overall samples ranging from 25 to 61 participants, with participant numbers as low as four per study in some age groups. As baseline utility values were rarely reported in the original studies, health-state

utility values applied in the model are based on absolute utilities. The use of Irish baseline utilities could also potentially overvalue the decrement associated with HZ or PHN as the Irish baseline values are higher than those from other countries,[324, 325] thereby biasing results towards vaccination. The sensitivity of the results to changes in the utility values for both PHN and HZ were highlighted in the OWSA. However, when values were set at the lower range (indicating greater loss in QALYs) in the OWSA, none of the HZ vaccination strategies were cost effective at a WTP threshold of €45,000 per QALY.

The base-case analysis conducted from the societal perspective captured the productivity loss associated with absence from paid work for those with HZ; the scenario analysis also included the productivity loss for those with PHN. There is potential for further productivity loss for those who require time off from paid work to care for adults with HZ and or PHN. However, there is substantial uncertainty regarding the proportion that need care, the proportion of these carers that are in paid employment, and the length of time off work. Given this uncertainty, these analyses did not include a productivity loss for carers and as such, the societal burden of HZ and PHN may have been underestimated in the model.

6.4.3 Conclusions

Based on the economic evaluation of HZ vaccination presented, the current evidence suggests that HZ vaccination does not represent an efficient use of healthcare resources. Although the vaccine has been demonstrated to be effective, there is also evidence of waning immunity. Additionally, while resource use associated with HZ and PHN in primary care is not insignificant, hospitalisation rates for HZ are low. When these costs and outcomes associated with HZ are modelled and vaccination is introduced, the results suggest that at the base-case vaccine price (€151.00) used in the model, HZ vaccination is not an efficient use of resources. The base-case results of the economic evaluation were robust to various sensitivity and scenario analyses. However, a threshold analysis identified that a significant drop in the vaccine price, to €30.00 per dose, would result in the ICERs for those vaccinated at 75, 80 and 85 years of age falling below €45,000 per QALY.

7 Organisational Issues

Key points

- The current adult immunisation programme in Ireland funds:
    - two annual seasonal vaccines (influenza and COVID-19 booster) as well as their administration
    - a pneumococcal vaccine which is typically administered as a once-off. While the vaccine is funded, those without a medical card or GP visit card must pay for vaccine administration, with the individual required to pay the full cost if it is accessed through a pharmacy.
- The RZV vaccine is a two-dose vaccine, but can be co-administered with other vaccines in the adult programme. Co-administration of the RZV vaccine with another vaccine in the programme:
    - would reduce the overall number of vaccine-related healthcare visits, potentially reducing the burden on patients and healthcare providers
    - could impact future uptake of the seasonal vaccines, given the potential for increased side effects with vaccine co-administration
    - would likely still necessitate an additional visit given the licensed indication to administer both doses of the RZV vaccine within a six-month window.
- Similar to the existing vaccines in the adult programme, RZV vaccination can be accessed through GP practices and community pharmacies. Over 70% of community pharmacies administer vaccines reimbursed through the HSE programmes.
- A decision to fund the RZV vaccine as part of the adult programme could have significant financial and logistical implications depending on the population group for whom the vaccine is funded. For example, a staggered roll-out approach to RZV vaccination would likely be required if RZV vaccination was extended to all individuals included in the NIAC recommendations.
- There is uncertainty surrounding the potential uptake of the vaccine given the wide range of uptake estimates for other vaccines in the adult immunisation programme and for RZV uptake internationally. For those who do not hold medical cards or GP visit cards, uptake may be lower if the cost of

administering the vaccine is passed on to the patient as is currently the case with the pneumococcal vaccine.

- If a decision were made to fund RZV, consideration would need to be given to:
    - defining priority groups for vaccination if demand were to exceed supply.
    - an information campaign to clearly indicate who is eligible for the vaccine and how to avail of it through the adult immunisation programme. For immunocompromised adults aged 18 and older, this may include engagement with clinical specialists in tertiary services to support uptake in identified subgroups.
    - the additional steps required to track and contact people about their second dose given the two-dose schedule.

7.1 Introduction

The aim of this chapter is to provide an overview of the potential organisational issues associated with the addition of herpes zoster (HZ) vaccination to the adult immunisation programme in Ireland.

7.2 Current adult immunisation programme

The vaccination programmes for vaccines which are routinely offered to adults in Ireland are described in Chapter 2. There are three vaccines in the adult immunisation programme: influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23), and COVID-19 booster vaccine (for those who have completed their primary immunisation schedule). All vaccines are provided both in pharmacies and general practices. The influenza vaccine and COVID-19 booster are provided free of charge to eligible populations. For PPV23, the vaccine is free in a GP setting only, and a consultation fee relating to the administration of the vaccine is charged for those without a GP visit card or medical card.[91] The cost of a consultation varies across providers as they have discretion to set their own fees. Those who chose to avail of the PPV23 vaccine in a pharmacy incur the cost of both the vaccine and the administration fee.

Both the influenza and the COVID-19 booster vaccines are seasonal vaccines typically administered annually as a single dose. PPV23 is generally given only once. Recombinant zoster vaccine (RZV) can be given concomitantly with non-adjuvanted inactivated seasonal influenza vaccines, the COVID-19 mRNA vaccine, and the

PPV23 vaccine.[21] The vaccines should be administered at different injection sites. Unlike the other vaccines in the programme, RZV requires two doses. The recommended interval between doses is two months, however the second dose can be administered between two and six months after the first dose.[21]

The adult immunisation programme is coordinated by the National Immunisation Office (NIO).[312] The HSE established the NIO in 2005 as a coordinating unit to ensure standardised implementation of all publicly funded immunisation programmes (primary childhood, school, seasonal influenza and others as required). In addition to the coordination of immunisation programmes, the NIO is also responsible for managing vaccine procurement and distribution and developing training and communication materials for health professionals and the public. Vaccine procurement accounts for over 90% of the NIO's budget and, since 2005, purchase of all vaccines for national programmes has been centralised and managed by the NIO.[312] Distribution of all vaccines under validated cold chain conditions (essential for vaccine potency) is provided by the HSE National Cold Chain Service with overall management, monitoring and control by the NIO.

7.3 Estimated number of eligible adults

RZV is licensed to prevent HZ and post-herpetic neuralgia. In Census 2022 there were 1.7 million people in Ireland aged 50 years and over,[157] representing a 17% increase in the size of this cohort since Census 2016.[158] The budget-impact analysis (BIA) in Chapter 6 modelled the budget impact associated with reimbursing the vaccine for a range of single-age year groups. Table 7.1 shows the estimated eligible population for the age groups considered in the economic analysis (Chapter 6). A range of plausible uptake scenarios were explored in the BIA (Chapter 6). A more detailed discussion on likely uptake rates is included in section 7.6.

Table 7.1. Number of eligible adults in the general population

Age (years)	Population in 2022
50	72,249
55	62,916
60	57,518
65	50,083
70	43,150
75	35,767
80	22,847
85	14,457

Source: Central Statistics Office[157]

RZV is also licensed for adults aged 18 years and older considered at higher risk of developing HZ. NIAC has identified subgroups for whom they specifically recommend immunisation or for whom they recommend that immunisation should be considered. [8, 9] These include:

- HSCT (haematopoietic stem cell transplantation) recipients aged 18 years and over
- patients aged 18 to 49 years at high risk of HZ due to specified immunocompromising conditions (that is, solid organ transplant recipients, those with haematological malignancies and those with advanced or untreated HIV (CD4 count <200 cells/µl) due to high risk of HZ) for whom immunisation should be considered, in conjunction with their treating specialist
- adults aged 50 years and older at increased risk of HZ due to immunocompromising conditions.

Chapter 3 provides a detailed breakdown of the estimated number of individuals in these additional groups, with the total estimated to be in the region of 100,000 individuals. In the event that RZV is made available to both specified at-risk subgroups and to the general population in a specific age group, some individuals may be eligible based both on age and at-risk immunocompromising conditions. Combining the age-based and at-risk population figures may represent a small over-estimate of the eligible population. It is also possible that reimbursed access could be restricted to one or some of the at-risk population groups.

7.4 Addition of HZ to the immunisation programme

If RZV is added to the adult immunisation programme, one or both doses may be given at the same time as another vaccine in the immunisation programme. There may be efficiencies for both patients and providers in coinciding RZV vaccination with other visits in the adult immunisation programme as it would reduce the number of healthcare appointments required. Vaccinating individuals at age 65 to coincide with the administration of influenza and pneumococcal (PPV23) vaccines might offer logistical advantages, potentially streamlining operations to support greater efficiency and increase uptake. Given the scheduling of the seasonal vaccines (influenza and the autumn-winter COVID-19 booster) and the typical once-off administration of PPV23, it is unlikely that both doses of RZV would be co-administered with another vaccine. As noted in section 7.2, the recommended interval between RZV doses is two months; however, if flexibility in the vaccination schedule is necessary, the second dose can be administered between two and six months after the first dose.[21] Therefore, even if the first dose of the vaccine is given alongside the seasonal influenza or COVID-19 vaccine, then the second dose will need to be given at a separate appointment. In this case, an additional GP or pharmacy visit would be required. Scheduling HZ vaccination during the summer months may offer an opportunity to manage workload.

All three vaccines currently available to the general adult population (influenza, COVID-19, PPV23) are available either through a GP or pharmacy; however, the full cost must be paid by the individual if PPV23 is accessed through a pharmacy. Community pharmacies were first included in the HSE immunisation programmes in 2011, accounting for 4.2% of the influenza vaccines administered as part of the National Seasonal Influenza Programme for that year. The number of participating pharmacists has increased year-on-year. For the 2022 to 2023 influenza season, over 70% of community pharmacies (n=1,344) are reported to have taken part, with 29% of all influenza vaccinations for the programme administered by community pharmacists.[326] Those aged 65 years and older and those in medical at-risk categories are well represented among those availing of vaccination in pharmacy setting. During the 2022/2023 influenza season, of those who received the influenza vaccine in a pharmacy, 26% were aged 65 years and over, and 19% were classified as medically at risk.[326] In the 2023/2024 season, to date, just over one-third of COVID booster vaccines have been administered in pharmacies.[327] It is recognised that there are GP shortages in Ireland, particularly in rural areas, and the HSE has estimated that approximately 1,600 new GPs are required by 2028.[328] Increasing the number of GP visits required for adult immunisation would potentially impact on GP practices that are already overburdened, increasing their workload and affecting their ability to provide a full service to existing patients and accept new patients. It is

expected that the burden for GP practices would fall on GPs for the initial consultation about suitability/eligibility for vaccination and potentially vaccine administration, on administration staff for coordination and reimbursement protocols, and on practice nurses for administration of the vaccine. Given that there has been good uptake of other vaccines provided through pharmacies, the availability of RZV through this route should partly mitigate the impact on GP services. Similar resource burdens are expected in pharmacies. Additionally, if vaccination is limited by the age of the recipient, the workload is distributed across the year rather than being concentrated at a particular time of year, as occurs in seasonal programmes. Of note, in England and Wales, a longer dose interval is being recommended (6 to 12 months) for operational reasons.[79]

Additional steps would be required to track and contact people about their second dose. The existing COVAX and PharmaVax IT portals, which are currently used to manage other adult vaccinations, could potentially be adapted for this purpose.[329, 330] Irrespective of its funding status, recording vaccine administration in a national vaccination recording system such as the HSE-COVAX would enable all healthcare professionals to have visibility of a patient's vaccination history.

7.4.1 Cost to recipient

As noted in section 7.2, there are policy differences in terms of the reimbursement of vaccines included in the immunisation programme for the adult population. For example, the cost of administration is currently passed on to recipients of the pneumococcal vaccine who do not have a medical card or GP visit card. If a decision is taken to reimburse RZV vaccination, a policy decision may be taken to reimburse both the vaccine and the administration cost or to reimburse the vaccine cost only. This may have implications for uptake (section 7.6). If the cost of administration is passed on to the recipient, this will likely vary by provider as they will be free to set their own consultation charge, potentially leading to inequities in access (Chapter 8). All those aged over 70 years are entitled to register for a GP visit card, so this age cohort will not need to pay any out-of-pocket administration charge.[331]

7.4.2 Catch-up programme

Given the large number of people who would be potentially eligible for vaccination, it is likely that, if HZ vaccination is added to the adult immunisation programme, a particular age group or number of age groups will need to be targeted each year. Internationally, countries have taken a varied approach to vaccine rollout as described in Chapter 2, with some countries implementing a catch-up programme for those who would otherwise miss out on vaccination. If a particular age year is targeted, for example those aged 65 years, then consideration could be given to a

phased catch-up programme for those aged 66 years and over. However, a catch-up programme would ultimately lead to a greater budget impact than that indicated in Chapter 6, and there would be additional demand for GP and pharmacy visits. Of note, RZV vaccination of the general population was found to be not cost effective at willingness-to-pay thresholds of €20,000 and €45,000 per quality-adjusted life-year (QALY) gained, irrespective of the age group considered (range €127,824 to €979,815). On this basis, the addition of catch-up programme would also not be cost effective. A cost-effectiveness analysis was not undertaken with respect to identified sub-groups at higher risk of HZ. Should a decision to be taken to restrict vaccine reimbursement to one or more of these subgroups, there would likely to be a lower requirement to phase implementation given the smaller numbers of individuals involved, and therefore a catch-up programme would be less relevant.

7.4.3 Impact on uptake of existing vaccine

EMA marketing authorisation for the approved RZV vaccine allows for its co-administration with the other vaccines currently listed on the adult immunisation programme (unadjuvanted inactivated influenza vaccine, COVID-19 vaccines, PPV23). It is noted that the immune responses of the co-administered vaccines is not impacted, but the frequency of systemic adverse events associated with RZV is increased relative to when it is administered alone.[21] Consideration should be given as to whether a policy of co-administration would impact the uptake rates of the vaccines currently in the programme. A large USA study (n=89,237) examined the impact of concurrently receiving RZV alongside seasonal influenza vaccination.[332] Those who received RZV vaccine alongside their influenza vaccine were less likely to get the influenza vaccine the next year; adjusted odds ratio 0.74 (95% CI 0.71 to 0.78). The impact of concomitant RZV-influenza vaccination on uptake of influenza vaccination the next year was statistically significant in all subgroups analysed including, age and prior receipt of the influenza vaccine.[332] As influenza is an infectious disease, maintaining high uptake rates of this vaccine may be preferable.

7.5 Resources

An expansion of the adult immunisation programme in Ireland to include HZ vaccination would have resource implications for the health service as a whole. The BIA (Chapter 7) aimed to capture these resource implications over the short term and to estimate the incremental costs to the health service of adding HZ vaccination to the adult programme. It included the cost of the vaccine, organisational costs associated with vaccine administration for both GP practices and pharmacies, the cold chain service, education and communication about the programme, as well as costs averted due to a reduction in hospitalisations for HZ.

7.5.1 Staff

Inclusion of HZ vaccination in the adult immunisation programme may require additional staff in certain circumstances. An additional GP visit or pharmacy visit will likely be necessary and so resources might be redeployed from other practice and pharmacy activities and require backfill. Administration of an additional vaccine at an existing appointment may also place an additional burden on the GP practice or pharmacy team, both in terms of vaccine delivery and the administrative burden associated with obtaining consent, dealing with queries and concerns, and recording the vaccine administration on the appropriate system. However, the fee provided by the HSE to GPs and pharmacies for administering the vaccine may facilitate the recruitment of locum staff to ease the burden during busy vaccination periods.

In Chapter 6, it was estimated that following the introduction of HZ vaccination and assuming 50% coverage, the predicted reduction in HZ cases over the time horizon of the model ranged from 11.5% if vaccination commenced at age 60 or 65 years to 3% if vaccination commenced at age 85 years. Given this estimated reduction in the number of HZ cases, there is potential that the additional work load for GP practices associated with administering the RZV vaccine would be partially offset by a reduction in GP consultation rates for HZ as well as a reduction in GP consultation rates associated with diagnosing, treating and managing PHN. Over time the number of hospitalisations for HZ should also reduce, decreasing the burden on secondary healthcare services.

7.5.2 Vaccine storage and handling

RZV is required to be stored and transported between +2°C and +8°C (Chapter 2). This is the same as the other vaccines administered in the adult immunisation programme. Cold chain procedures must be followed. The NIO is responsible for managing vaccine procurement and distribution including coordinating the National Cold Chain Service which is provided by a contracted distributor with the vaccines delivered directly to GP surgeries, pharmacies and local HSE offices.[312] An estimated cost for the RZV cold chain service was included in the BIA. Given this existing service, organisational issues relating to storage and distribution associated with any expansion of the immunisation programme to include RZV were considered to be minimal. However, an additional fridge may be required by certain GP practices and pharmacies, which would require an initial investment by the GP practice or pharmacy.

7.5.3 Training

The Pharmaceutical Society of Ireland outlines the training that pharmacists must undertake to be permitted to supply and administer vaccines.[333] Along with a

standard training programme for vaccination, pharmacists must complete training specific to the HZ vaccine; this training is valid for two years.[333] The training for the HZ vaccine takes approximately two hours to complete.[334] Accredited training programmes for pharmacists are readily accessible. Should the HZ vaccine be added to the national vaccination programme, upskilling the pharmacist population to administer the vaccine would be straight forward and would ensure a considerable trained workforce is available. Current uptake of HZ vaccination is limited given that individuals must pay for the vaccine out-of-pocket. Expansion of the immunisation programme to include reimbursement of the HZ vaccine may therefore result in increased uptake of the HZ-specific training. However, as highlighted in section 7.4, over 70% of community pharmacies already participate in administering vaccines reimbursed through the HSE programmes; therefore, a large proportion of community pharmacists have already completed the core training required for the administration of any vaccine.

GPs who intend to administer the vaccine will also need to complete additional training, which will mean time away from clinical practice.

7.5.4 Vaccine availability

As outlined in Chapter 2, only two HZ vaccines are licensed by the EMA and only one will be continued to be marketed in Ireland (RZV). As more countries start using the vaccine, there is potential for vaccine shortages should international demand exceed available manufacturing capacity. Following its approval in 2017 vaccine shortages were documented for RZV in the US in 2018 and 2019 due to increased demand arising from changes to the US Centers for Disease Control and Prevention (CDC) recommendations. If RZV were funded in Ireland, it is possible there could be pent-up demand for the vaccine on programme launch leading to pressure on vaccine administrators. Careful programme planning would be required to manage expectations and minimise any logistical issues.

Given a single supplier of RZV, consideration should be given to what would happen in the case of vaccine shortage including which groups would be prioritised and whether there should be catch-up vaccination for those who missed out during periods of vaccine shortage. Preventing vaccine shortages, which can arise for multiple reasons including manufacturing or production problems, has been identified as an international public health priority issue.[335] As outlined in Chapter 4, there are several ongoing trials of HZ vaccines which could become alternatives to RZV. If alternatives become available, this could alleviate supply issues.

7.5.5 Information and awareness

All information materials for the general public are developed and distributed by the NIO who also manage the national immunisation website www.immunisation.ie.[336]

An information campaign is an important component of any change to the adult immunisation programme. The purpose of the campaign would be to educate the eligible population on the potential risk of complications from HZ, allay any concerns regarding the safety or efficacy of the vaccine and enable informed consent. To support such a public awareness communication campaign, consideration would also need to be given to an educational programme for GPs, pharmacists and front-line nursing staff given their important role both in vaccine administration and as a trusted information source for other vaccines. An estimated cost for education and communication was included in the BIA.

If a decision is made to fund RZV for specific at-risk groups, consideration could be given to a more tailored information campaign which targets tertiary care services and chronic disease management programmes. Clinical staff in tertiary care services would have regular contact with HSCT and solid organ transplant recipients and those with HIV, and so could support a targeted information campaign. The HSE has a number of chronic disease management programmes that it funds in primary care for adults with specific conditions. These programmes entail two free structured reviews with the practice nurse and GP in every 12 month period to support ongoing treatment and management. These may provide an opportunity to raise awareness and improve vaccine uptake in enrolled individuals who are also eligible for free HZ vaccination. For example, the Diabetes Cycle of Care for those with T2D specifically includes a review of immunisation status as part of the scheduled review.[337]

7.6 Anticipated vaccine uptake

The current uptake levels of RZV in Ireland, which is at full cost to the recipient, the uptake of RZV internationally and the uptake of other relevant adult vaccines are considered here. RZV was first marketed in Ireland in April 2022 and is available privately with the cost absorbed by the recipient. For the period April 2022 to December 2023, the manufacturer has estimated almost 18,000 doses have been administered.[338] Considering the eligible Irish population of all adults age 50 years and older (1,696,153 Census 2022),[157] this equates to approximately a 0.5% uptake.

7.6.1 Uptake of other vaccines in Ireland

7.6.1.1 PPV23

Published data suggest that uptake of the PPV23 vaccine in Ireland is low, with vaccine uptake in the older population noted to be more than double that reported

in younger at-risk groups. National telephone surveys were conducted in 2006, 2010 and 2013.[339] The 2013 survey noted that, among those for whom pneumococcal vaccine was recommended, 16% (41/250) (95% CI: 12%-21%) of those aged 18 to 64 years and 36% (98/271) (95% CI: 30%-42%) of those aged 65 years and older reported ever being vaccinated.[339] More recent published data on pneumococcal vaccination uptake in Ireland were not identified.

Several small studies have also assessed the uptake of PPV23 in specific groups. Over a three-month period after influenza season 2009/2010, a combination of retrospective medical record review and patient questionnaire was undertaken in a diabetes outpatient clinic (n=200). Reported lifetime uptake rate of pneumococcal vaccine was 22%. Significant predictors of pneumococcal vaccine uptake were listed as GP recommendation (odds ratio=63; 95% CI: 10-388), and chronic kidney disease (odds ratio=22; 95% CI: 1.5-312).[340] An audit of general practice data from 2017/2018 found a 40.6% uptake of the pneumococcal vaccine in patients with diabetes.[341]

In an audit of patients attending Irish rheumatology clinics and using immunosuppressive drugs (n=110), vaccination uptake was as follows: influenza alone (34%), pneumococcal alone (11%), both pneumococcal and influenza vaccination (11%); therefore, 56% had one or both vaccines.[342] In a second study of patients attending a rheumatology unit (n=92), vaccination uptake was also reported to be low; 32.6% patients received both the pneumococcal and influenza vaccines, and 25% received only one vaccine.[343] The main reason for low uptake was noted to be lack of awareness of vaccine availability.[343]

Uptake of the pneumococcal vaccine adults in Ireland is low compared with the paediatric schedule (27–36% vs 81–92%). This may be because pneumococcal vaccination is part of the primary childhood immunisation schedule whereas in adults access is more opportunistic and is not always free.[344] While uptake rates are monitored as part of the childhood schedule, there is currently no similar scheme for routinely monitoring pneumococcal vaccine uptake in adults.

7.6.1.2 Influenza

From the 2010-2011 season to 2019-2020 (the last season before the onset of the COVID-19 pandemic) the uptake rate of the influenza vaccine has ranged from 54.5% (2016-2017 season) to 68.5% (2018-2019 season).[345] During the 2020-2021 influenza season, the uptake rate in those aged 65 years and older increased to 70.5% and has remained above 70% to date. For the 2021-2022 influenza season, the uptake rate in this age group was reported to be 75.4% and for the 2022-2023 influenza season it was 76.5%.[176] These figures reflect the administration of

influenza vaccines across all settings — that is, GP practices, community pharmacies, long-term care facilities and healthcare work clinics. The 2022-2023 uptake rate is the first year in which the vaccination of healthcare workers and long-term care facility residents was also accounted for; this addition may account for some of the increased uptake in the 2022-2023 influenza season.

7.6.1.3 COVID-19

As for the other vaccines in the adult programme, it is challenging to predict likely uptake of a long-term immunisation programme for HZ based on patterns of COVID-19 vaccine uptake. Booster uptake data are provided here, but it is unclear if this uptake rate would be applicable to HZ vaccination. The uptake of autumn 2023 booster was 20.3% in the 50-69 years age group and 51.7% in those aged 70 years and older.[327]

7.6.2 International uptake data

RZV was first licenced for use in the USA and EU in 2018. It was not marketed or reimbursed in many countries until recently (Chapter 2). Therefore, uptake data for RZV are limited.

HZ vaccination rates in the UK have fluctuated over time. Shingles vaccine coverage in the general population (aged 70 years) was 48.3% in 2016/17 representing a 13.5% decline since the start of programme (54.9% in 2015/16, 59.0% in 2014/15, 61.8% in 2013/14).[346] However, more recent data from the UK shows that cumulative coverage for all eligible adults increased year-on-year through opportunistic vaccination, as once an adult becomes eligible (currently at aged 70) they stay eligible until aged 80.[347] A cross-sectional survey of 372 UK participants aged 65 to 92 years compared uptake of HZ influenza and pneumococcal vaccination.[348] Considerably more participants had received the influenza vaccine in the previous 12 months (83.6%) relative to having ever received the pneumococcal (60.2%) and HZ vaccines (58.9%). These data related to the live vaccine, ZVL, which only required one dose. A much larger cross-sectional study of adults in England (n=2,054,463) found 53.4% of those aged over 70 years had been vaccinated against HZ.[349] There was generally lower vaccination uptake among more deprived individuals, people living in larger household sizes (three or more persons) and those with fewer health conditions. Again, these data related to ZVL.

Data on uptake rates for RZV were identified from the USA only. A retrospective cohort study collected data for those aged 50 to 64 years in 2018/2019[350]. In January 2018, the US CDC recommended the preferential use of RZV over ZVL due to higher efficacy against HZ and its sequelae, and longer-lasting protection. In the first two years of this recommendation, the cumulative incidence of RZV initiation

was 10.0%. Incidence increased with age and number of medical office visits, and was higher among women, urban residents, high-deductible insurance beneficiaries, and those who were immunocompromised compared to the general population. Among immunocompromised adults, RZV initiation was highest among those with HIV and primary immunodeficiencies. Of those who initiated RZV, 89.5% received both doses. RZV completion was highest among those who received the first dose at a pharmacy.[350] Although ZVL was no longer preferentially recommended, some people may have received this vaccine instead and are not counted in this HZ vaccine uptake rate. A second study from the USA also assessed adherence rates for the second dose of RZV.[351] Among 726,352 adults included, the adherence rate was 71.8%.[351]

A systematic review published in 2023 reported on willingness to vaccinate for HZ.[352] The pooled HZ vaccination willingness rate was 55.74% worldwide. The main reasons for the unwillingness to receive the HZ vaccine include low trust in the effectiveness of the HZ vaccine, concerns about safety, low perceptions of disease risk, financial concerns, and unawareness of the availability of the HZ vaccine. Healthcare worker recommendations were also correlated with a greater likelihood of receiving an HZ vaccine.[352]

A scoping review published in 2022 identified predictors of pneumococcal vaccine uptake in older adults aged 65 years and older in high-income countries.[353] Factors identified which increased vaccine uptake included receiving influenza vaccination and healthcare providers either recommending, prescribing, or providing information on pneumococcal vaccination. Barriers included financial cost of pneumococcal vaccine, a lack of knowledge, financial and logistical issues, and concerns with vaccine safety and effectiveness.[353]

A cross-sectional survey of 372 UK participants aged 65 to 92 years assessed awareness and uptake of the influenza, pneumococcal, and shingles vaccines.[348] Participants exhibited greater uptake and awareness of the influenza vaccine relative to the pneumococcal and shingles vaccines. Psychosocial factors were associated with uptake rates of each of the three vaccines such as mistrust of vaccine benefit, and worries about unforeseen future effect. Greater concerns about commercial profiteering were also associated with lack of uptake of the pneumococcal and shingles vaccines.

A systematic review and meta-analysis of the impact of pharmacist-involved interventions on immunisation rates including influenza and HZ found that pharmacist involvement as administrator, advocator, or both roles has favourable effects on immunisation uptake, compared with usual care or non-pharmacist-

involved interventions, especially with influenza vaccines in the United States and some high-income countries.[354]

7.7 Discussion

In Ireland, there are three vaccines funded for the general adult population as part of the adult immunisation programme. If a decision is taken to also fund HZ vaccination, it is assumed that this will be coordinated by the NIO with consideration given as to how to optimise uptake in the context of the other vaccine recommendations.

Notable organisational issues relate to the potential co-administration of the vaccine with other vaccines in the programme, implications for uptake of other vaccines, and resources for ensuring uptake of and administration of the second dose. The RZV vaccine may be administered with any of the other vaccines in the adult immunisation programme — although unlike other vaccines in the programme, RZV is a two-dose vaccine. Combining the administration of RZV with another vaccine would negate the need for one additional healthcare appointment. However, due to the higher incidence of adverse events, there is evidence that co-administration could result in reduced future uptake of the seasonal vaccine given alongside RZV.[332]

The uptake rate of the other vaccines in the Irish adult immunisation programme were presented in this chapter to inform potential uptake of HZ vaccination. Uptake of the pneumococcal vaccine is low compared to other vaccines in the adult immunisation programme (27-36% versus 20.3%-76.5%). This may be because access to the pneumococcal vaccination is more opportunistic compared with targeted seasonal campaigns for influenza and COVID-19 vaccination which serve to raise awareness. Uptake of the pneumococcal vaccine may also be impacted by the potential out-of-pocket costs for vaccine administration for some individuals, whereas COVID-19 boosters and annual influenza vaccination is provided free-of-charge to populations relevant to this HTA — that is, those in the general population aged 65 years and older, and those in medical at-risk groups.

Previous work by HIQA identified the barriers and facilitators to influenza vaccination uptake and these are relevant to any changes being considered for the adult immunisation programme.[355] The evidence relating to barriers and facilitators to vaccination uptake can be summarised into 10 themes: perceived risks and or benefits of vaccines; access and or contextual factors; psychological and or internal factors; perceived risks and or susceptibility to influenza; perceived responsibility; social influences; past behaviours and or experiences; knowledge; sociodemographic factors; and health behaviours. The extent to which these barriers and facilitators

might influence uptake in an HZ vaccination programme would depend on how it is implemented — for example, whether there is a cost to the recipient, and the age at which the vaccine is provided. As people age, they will be increasingly likely to either have had an episode of HZ or to know someone who has, and this may well influence their perception of the benefit-harm balance of vaccination.

Recent information campaigns have meant that many Irish people are aware of HZ and the associated complications. Therefore, if a vaccine were to be made available, there could be strong demand at the launch of the programme. This could pose logistical issues for those who are administering the vaccine. Along with other potential causes of vaccine shortage, this would need to be accounted for by vaccine administrators and programme planners. An information campaign would be required to clearly indicate who is eligible for the vaccine and how to avail of it through the adult immunisation programme. This may include engagement with clinical specialists in tertiary services, and primary care services, to support uptake by those who are eligible on the basis of being in a defined at-risk subgroup.

Over the longer term, the additional resources required for vaccination should be offset by the reduced incidence of HZ and corresponding impact on associated healthcare need. A review of the Zoster Vaccine Live vaccination programme in England found large and prolonged reductions in HZ and PHN consultations and hospitalisations in the five years post-implementation.[356] Output from our economic evaluation (Chapter 6) shows that case numbers of HZ would be reduced by vaccination. However, it is unlikely that numbers of GP appointments prevented by vaccination would outnumber the number of vaccination appointments required.

8 Ethical and social considerations

Key points

- The purpose of vaccination is to prevent or reduce the spread of infectious disease. In terms of the benefit-harm balance, there is clear and consistent evidence that HZ vaccination is effective at reducing incidence of HZ.
- The evidence suggests that RZV vaccination is safe. While mild local and systemic reactions, such as pain at injection site, fatigue and myalgia, are common, serious adverse events are rare.
- Policy makers have a duty to ensure equitable allocation of resources. Reallocation of resources has the potential to affect the existing healthcare system as it may divert resources from other effective treatments provided within the overarching healthcare budget. The introduction of HZ immunisation would create demand for primary care resources, possibly causing displaced care initially. However, this shift could transition the demand from treatment-focused care to a more preventive care-oriented approach.
- In terms of respect for autonomy, in the context of HZ, vaccination entails providing individuals with clear and comprehensive information about the vaccine's implications, both for receiving and abstaining, including an understanding of associated risks, while also ensuring healthcare professionals can seamlessly integrate vaccination activities into their daily workflows without compromising care quality.
- Evidence from this HTA highlights that, based on current data, vaccinating adults in the general population over the age of 50 years against HZ is not cost effective and is associated with a substantial budget impact. The healthcare budget is finite; including HZ vaccination in the adult immunisation programme could require reallocation of resources, potentially impacting the existing healthcare system by diverting resources from other more cost-effective interventions or from the overall healthcare fund. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity costs (the value of the next best alternative forgone) of new investments are considered. This may prove difficult as there may be many competing claims requiring prioritisation of care. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens.

- The timing of the assessment impacts on the available data to evaluate the long-term clinical effectiveness of HZ vaccination. In contrast to the ten-year randomised controlled trial evidence, there is currently no long-term real-world effectiveness data on waning beyond a four-year timeframe. It is important to offer individuals transparent and accurate information about the limited long-term effectiveness data as part of the informed consent process.

8.1 Introduction

This chapter discusses the ethical issues that should be considered in relation to the expansion of the adult immunisation programme to include herpes zoster (HZ) vaccination. This chapter was broadly developed in line with the structure described in the European network of HTA (EUnetHTA) Core Model.[357] The ethical issues raised around a technology must be assessed in relation to the prevalent social and moral norms relevant to the technology. An ethical analysis as part of an HTA involves exploring the possible consequences of implementing and not implementing the health technology under consideration. This section also examines the ethical issues related to the HTA itself.

While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent, and, as far as possible, non-coercive. Governments can help prevent or reduce the spread of infectious disease through funding population-level vaccination programmes. Although it is reasonable for a State to aim for high vaccination rates, the balance of benefits and harms to individuals and the wider population should be continuously reviewed. It must also be recognised that individuals have the right to opt out of such immunisation programmes. As a result, there may be conflict between individual and public interests, and a balance must be struck between competing values and principles. In the context of this chapter, the technology is an HZ vaccination programme aimed at adults in the general population aged 50 years and older and for those aged 18 and older who are at increased risk of HZ due to an immunocompromising condition.

8.2 Benefit-harm balance

8.2.1 Burden of disease and epidemiology

The burden of HZ disease and epidemiology was discussed in Chapter 3. HZ, which is commonly known as shingles, is typically recognised by a painful blistering rash on the torso. HZ is caused by reactivation of the varicella zoster virus (VZV). Primary infection with VZV results in varicella (chickenpox) which typically presents in

children. After varicella infections resolve, the virus remains and becomes latent in the body's nervous system. The virus may reactivate after a period of time, typically several decades later, resulting in HZ. HZ disease is characterised by a vesicular skin rash, often associated with acute pain and itching. Areas of skin around the torso (termed, thoracic dermatomes) are most frequently affected. These dermatomes are supplied by nerve connections from spinal nerves, and correspond to specific spinal segments. The lifetime risk of experiencing HZ has previously been reported as approximately 30%.[1] HZ mostly presents in patients age 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.[108] Morbidity associated with HZ increases with age, and the most common complication is post-herpetic neuralgia (PHN), with estimates reported by one systematic review ranging from 5% to more than 30% of HZ cases.[6] Those with PHN experience persistent pain in the area of the rash, with the potential to cause significant reductions in quality of life, activity, mood and sleep.[358] Of those who develop PHN, the pain may last for more than one year in over 30% of patients[6] and more than five years in 2% of patients.[359]

For many immunisation programmes, all or almost all of the target population are offered vaccination in the knowledge that perhaps only a small proportion will benefit. However, the case is different for vaccination against HZ, where many recipients will directly benefit. The benefit-harm balance must be considered at both the individual level and at the population level. The decision to be vaccinated is made by individuals, typically from the perspective of what the perceived benefit-harm balance is for them personally. The decision-maker, on the other hand, must consider the benefit-harm balance at the population level. Both perspectives are considered in this chapter. In an ideal scenario, the patient, family, healthcare professionals, healthcare system and wider society would all benefit from a technology without any harms. However, in reality, there is a risk of harm with every technology and this needs to be carefully balanced against the benefits.[357] Ethically, the impact of HZ vaccination extends across individuals and the healthcare system, emphasising the need for informed consent and positive health outcomes, while ensuring fair and equitable access to HZ vaccination.

8.2.2 Benefits and harms at an individual level

Numerous studies have been undertaken to determine the efficacy, effectiveness and safety of the recombinant HZ vaccine (RZV). The evidence generated by those studies was reviewed in Chapter 4. In this section, the benefit-harm balance is considered from an ethical perspective. A systematic review of efficacy and effectiveness of RZV was carried out as part of this HTA and is fully reported in Chapter 4. There is clear and consistent evidence that vaccination is very effective at

reducing the incidence of HZ. Vaccine efficacy was estimated at 92% based on the combined RCT data, and 70% based on observational data. However, data from one long-term study in the general population aged 50 years and over show that vaccine efficacy wanes by approximately 25% by year 10 from 98% to 73%. While exhibiting a reduction, vaccination continues to provide protection. Considering the age group being considered for vaccination, that is those aged 50 years and older, it is important to recognise the significance of waning immunity over time. Given the average life expectancy of over 80 years in Ireland, there is a need to temper expectation of life-long immunity and the potential need for booster doses, for example in those vaccinated before the age of 50. The vaccine is effective in those considered at increased risk of HZ aged over 18 years, although efficacy might be slightly lower in these populations than in the general adult population aged over 50 years.

Individuals with HZ can transmit VZV to someone who has not had varicella and is not immune (Chapter 3). If HZ vaccination is implemented, transmission rates of varicella may be reduced. HZ can be a debilitating condition that may require individuals to take time off work due to illness. By getting vaccinated and avoiding the onset of HZ, individuals are less likely to experience work disruptions, and avoid loss of societal productivity. Carers may also be required to take time off paid work while they help an individual recover from HZ, resulting in a further loss of societal productivity. Full-time carers often do not have the option of a contingency measure if they themselves get ill; an episode of HZ can entail interrupted care for those they support. The RZV vaccine contributes to an improved overall quality of life by preventing the pain, discomfort, and potential complications associated with HZ. This, in turn, allows individuals to continue their daily activities, including work, without the hindrance of a debilitating illness. While the majority of individuals recover completely within two to four weeks, a small proportion experience severe complications arising from HZ requiring hospitalisation, while others experience a protracted course and recurrent episodes. By preventing HZ and associated complications, RZV can contribute to lower healthcare costs for individuals as HZ can result in medical expenses related to GP visits and medications.

The potential benefits of vaccination must be balanced against the potential harms. A systematic review of the safety of RZV was carried out as part of this HTA (see Chapter 4). The evidence suggests that RZV vaccination is safe. While mild local and systemic reactions, such as pain at injection site, fatigue and myalgia, are common, serious adverse events (SAEs) are rare. Local reactions are reported by 74% to 84% of recipients, systemic reactions by 53% to 66%, and SAEs by 3.5% to 17%. These local and systemic reactions are generally transient and mild to moderate in intensity. There is no strong evidence to suggest that adverse reactions influence

completion of the two-dose schedule. As with other vaccines in the immunisation programme, HZ vaccine is not 100% effective: an individual might experience adverse effects and also go on to develop HZ. The evidence on the co-administration of RZV with other vaccines suggests that co-administration does not compromise the safety of the vaccines, although local and systemic reactions are typically more common when co-administered with another vaccine. RZV vaccine recipients must provide consent for administration of the vaccine and decide whether or not it is acceptable to expose themselves to the risk of an adverse event, and for judging how serious that event could be. A robust informed consent process ensures that this decision is made on the basis of clear, relevant, up-to-date information about the benefits and risks associated with the vaccine. The provision of appropriate and adequate information to recipients is even more important in light of the fact that anecdotal reports of harms can result in vaccine hesitancy and vaccine refusal.

Resilient immunisation programmes seek to maximise enablers to vaccination and minimise barriers by mitigating misperceptions and ensuring vaccine decisions are driven by evidence rather than fear. Co-occurrence of vaccination and a period of ill health may easily be perceived as being causally related, even though there may be no plausible mode of action to link the two events. The publication of a large volume of evidence refuting a link between the vaccine and a wide range of adverse events may be of little consolation to a recipient who believes they have been exposed to harm through vaccination. The concerns of people who have worries about the safety of the vaccine should be addressed appropriately. It is critical that in cases in which a vaccine is perceived by a recipient to have caused harm, these concerns are not dismissed. It is imperative to acknowledge the fact that recipients who believe they were harmed through vaccination are not inherently opposed to vaccination, as they consented to receiving the vaccine in the first place.

It is important to note that the benefits of HZ vaccination typically outweigh the potential harms for the majority of individuals, especially for those at higher risk of developing HZ or its complications.

8.2.2.1 Perceptions and expectations of herpes zoster vaccination

We were not able to identify Irish data on the perception of patients towards HZ vaccination. However, it should be noted that individuals aged 50 years and older and those aged 18 years and older at increased risk of HZ have paid privately to receive HZ vaccination, indicating that there is a baseline level of acceptance. Shingrix® was launched in Ireland in April 2022; data provided by GlaxoSmithKline show unit sales reached 4,749 doses for 2022 and anticipated unit sales is forecast to have reached 12,968 doses for 2023. This would correspond with 2,375 people

vaccinated in 2022 and 6,484 in 2023, assuming 100% dose compliance with the two-dose schedule.[338]

A 2011 study carried out in Denmark found that acceptance of zoster vaccination was reliant on public awareness about HZ and the treatment and preventive options available.[360] The study concluded that public awareness about HZ was poor. This study showed that people who have no experience with HZ underrate both its prevalence and impacts on patients' quality of life. Delayed treatment and low uptake of HZ vaccination may stem from such misperceptions. A French observational study showed a large majority 87.6% knew about HZ and 68.9% would agree to be vaccinated against HZ if they had risk factors, although only 10.1% were aware of the existence of an HZ vaccine.[361] A study aimed to assess the global willingness to receive the HZ vaccine and identify factors influencing vaccine uptake across World Health Organization (WHO) regions.[352] The analysis included 13 studies covering 14,066 individuals from eight countries in four WHO regions. The pooled global vaccination willingness rate was 56%, with 56% of adults aged 50 years and older expressing willingness. After receiving healthcare workers' recommendations, 75% of individuals were willing to get the HZ vaccine. Without HCWs' recommendations, the willingness rate dropped to 49%. A cross-country analysis of the perceptions and decision-making behaviour of older adults regarding vaccinations was conducted in 2019 to 2020 in four countries: France, Hungary, Italy and the Netherlands. It was reported that vaccines against influenza and tetanus were commonly known, while the awareness of vaccines against pneumococcal disease and HZ was low.[362]

8.2.3 Benefits and harms at a population level

8.2.3.1 Impact on existing national adult immunisation programme

The purpose of this HTA is to examine the impact of adding HZ vaccination to the national adult immunisation programme. The addition of the HZ vaccine to the programme would broaden the protection it provides and as such, may positively influence public perception. The addition of vaccines targeting diseases that affect adults promotes the concept of lifelong health and preventive care. The addition of the HZ vaccine would also provide an opportunity for public health campaigns and education, raising awareness about the importance of adults' immunisation and the risks associated with HZ.

Public perception of the programme could also be negatively impacted by the introduction of HZ vaccination. There may be perceived overload whereby individuals might feel that their immune system could be overwhelmed by receiving multiple vaccines, undermining the uptake of existing vaccines. The introduction of HZ

vaccination into the programme could impact on pharmacy and GP practices that are already overburdened due to insufficient capacity to meet demand. HZ immunisation require two doses, so additional pharmacy and or GP visits are required. Healthcare workers would need to be educated and trained to administer the new vaccine, including understanding the target population, dosing schedules and potential side effects. The costs associated with this and organisational impacts were considered in Chapters 6 and 7, respectively. If implemented, ongoing surveillance and monitoring systems would need to be in place to track vaccine coverage, identify adverse events and assess the overall impact on public health. Public awareness campaigns are crucial to inform adults about the importance of the new vaccine, addressing any concerns or misconceptions.

8.2.3.2 Wider societal impact

Attending vaccination appointments requires a time commitment. While co-administration with other vaccines in the adult programme is possible, an additional vaccination appointment would be required, given RZV's two-dose schedule. This would add to the burden on recipients and caregivers. However, this inconvenience could be counterbalanced by the fact that once vaccinated, the recipient would be less likely to develop HZ and therefore would not need to forego other activities given that the symptoms of HZ and its complications can take weeks or months to resolve. Due to the waning immunity associated with HZ vaccination, younger individuals in the immunocompromised cohort with a lifelong elevated risk of HZ, could need booster doses to maintain sufficient immunity. While there is evidence of waning, the need for booster doses following the primary vaccination schedule has not yet been established.[21] Many of the vaccine recipients could be older persons and require supportive care; consequently, vaccination would have the potential to prevent HZ and alleviate the burden on caregivers, leading to a more manageable caregiving experience. Families of those with HZ can be affected through caregiving responsibilities, and through family members needing to fill additional roles during the period of illness.[363]

The primary goal of adding a new vaccine to the programme would be to prevent additional vaccine-preventable diseases among adults, thereby improving overall public health. HZ vaccination can reduce the incidence, severity and complications of HZ disease, ultimately leading to a decrease in overall burden on healthcare systems.

When evaluating population vaccination programmes, a societal perspective captures benefits of vaccination including productivity gains where vaccination prevents disease and resulting absence from work due to illness. However, due to increasing

risk of HZ with increasing age but lower workforce participation with increasing age, the productivity gains are not substantial in the case of HZ vaccination.

8.3 Autonomy

8.3.1 Autonomy of vaccine recipients

The rollout of HZ vaccination for adults could have implications for the autonomy of vaccine recipients, particularly vulnerable adults. Autonomy refers to an individual's ability to make informed, voluntary decisions about their own healthcare. Autonomy is upheld when individuals have access to clear, comprehensive information about the vaccine, including the implications of both receiving and not receiving it, as well as the risks associated with the condition the vaccine seeks to prevent. This includes details about the vaccine's purpose, effectiveness, potential risks, and any alternatives. Adequate communication and education efforts are essential to ensure that vulnerable adults have the information they need to make informed decisions. This is particularly important for individuals who may face challenges in accessing healthcare information independently. Healthcare professionals should engage in open and respectful discussions, acknowledging the autonomy of vulnerable adults to either accept or decline the vaccine based on their values, preferences, and individual health circumstances. For individuals facing cognitive or decision-making challenges, healthcare professionals may need to assess their capacity to make informed decisions. In such cases, involving caregivers or family members while respecting privacy and confidentiality becomes crucial. Vulnerable adults may have specific concerns or questions related to the vaccine, such as safety concerns or potential interactions with other medications. Addressing these concerns empowers individuals to make autonomous decisions.

Individuals who would be eligible for the HZ vaccine are likely eligible for other vaccines, such as those for influenza and COVID-19, indicating that hurdles posed by HZ vaccination relating to the autonomy of the vaccine recipient are not unprecedented.

When an immunisation programme is expanded to include an additional vaccine, the associated health promotion and awareness campaigns can create public interest in the vaccine. Some individuals not eligible for the vaccination may still seek private access to the vaccine. Given evidence that approximately 6,500 individuals were vaccinated privately in 2023, it would be imperative to ensure that the information received through private access is consistent with that given as part of the immunisation programme.

8.3.2 Autonomy of healthcare workers

Healthcare professionals have a significant role to play as advocates for immunisation. The Guidelines for Vaccinations in General Practice in Ireland state that the GP should avail of every opportunity to promote vaccination[364]. Healthcare professionals are responsible for direct communication of health information to their patients, and their perception of vaccination programmes can therefore influence the attainment of the national immunisation programme objectives. If implemented, an HZ vaccination programme would potentially be available for various subgroups of people considered at increased risk of HZ. It would be essential to establish clarity regarding eligibility criteria for vaccination for any such subgroups.

The rollout of a new vaccination programme could impact healthcare workers' workload and time management. Autonomy in this context involves the ability to efficiently integrate vaccination activities into daily workflows without compromising the quality of care provided. The introduction of a new vaccine may impact resource allocation within healthcare settings. Autonomy in decision-making related to resource allocation involves considering factors such as vaccine supply, storage, and distribution in alignment with the overall vaccination programme. In the budget-impact analysis (Chapter 6), the maximum eligible population was approximately 168,000 people if all immunocompromised populations were included and general population vaccination was at age 50 years. Based on 50% uptake for the general population and 100% uptake for immunocompromised populations, it would translate into approximately 133,000 vaccinations in year one and 40,000 in each of years two to five. Organising a vaccine programme for this number of people would have significant resource implications. If HZ vaccination was added to the adult immunisation programme exclusively for immunocompromised patients, approximately 98,000 individuals would be eligible for vaccination in year one of the programme, with 5,200 eligible individuals per annum in years two to five.

8.4 Respect for people

Consideration would be required in relation to the potential impact of the implementation or use of the technology on human dignity; moral, religious or cultural integrity; and privacy. HZ is a common illness and therefore, if introduced, an HZ vaccination programme would benefit many of the adults who receive the vaccine. Certain religious or cultural groups may have a moral objection to immunisation, including HZ immunisation. It is essential for healthcare professionals to be aware of these perspectives and approach discussions with respect and cultural sensitivity. Vaccine hesitancy attracted increased attention throughout the COVID-19 pandemic. One factor that influences vaccine hesitancy is online misinformation.[365] Vaccine avoidance on these grounds could affect vaccine uptake rates, although it is unclear that HZ vaccination would give rise to a level of vaccine

avoidance over and above what might be observed for the other vaccines currently included in the adult immunisation programme in Ireland. Improving health literacy and providing accurate information about the safety and efficacy of vaccinations are crucial steps in addressing objections. Tailored educational programmes that consider the cultural and religious context can help dispel myths and misconceptions, empowering individuals to make informed decisions about their health.

It is important to respect an individual's privacy during the vaccination process. However maintaining privacy becomes a challenging task, especially in long-term care facilities, where residents may experience reduced privacy during vaccination clinics organised to administer vaccines to them. While this concern extends beyond this specific vaccine, it necessitates careful consideration. There are considerations to take into account in the pharmacy setting also. Pharmacies in Ireland have in place a patient consultation area with the purpose of discussing in private any health matters or concerns patients may have. The Pharmaceutical Society of Ireland has published guidelines in relation to patient consultation areas in retail pharmacy settings — these areas are used for private consultations including vaccination administration.[366] Therefore, patients and pharmacists can discuss medical eligibility and consent information, as required, in a private matter. An opportunity is provided for patients to supply further information or ask questions privately within the consultation area where the vaccine administration takes place. There is a precedent with other vaccinations on the adult immunisation programme. Decisions or actions regarding an HZ vaccination programme may be influenced or guided by the past experiences or protocols associated with other vaccinations in the adult immunisation programme. Appropriate General Data Protection Regulation (GDPR) practices should also be adhered to in all vaccination settings.

8.5 Justice and equity

The principle of justice refers to the requirement for people to be treated fairly and equitably both in terms of the distribution of benefits and burdens, as well as the recognition of people's rights and responsibilities.[367] In relation to population level healthcare decisions, opportunity costs are an essential factor to consider. Consideration needs to be given to the total size of these opportunity costs as well as understanding who will bear the consequences of these costs.[368] Currently, the HZ vaccine is available in Ireland to those who are willing to pay privately for it. However, not all adults can afford the vaccine, and not all are aware that it exists. The addition of HZ vaccination to the adult immunisation programme in line with NIAC recommendations would ensure that the vaccine is available to all of those eligible to receive it. Of note, in contrast to the paediatric and schools-based

immunisation schedules, a vaccine administration fee may apply in relation to the administration of vaccines in the adult immunisation programme. Specifically, only those with those a GMS or GP visit card are exempt from paying an out-of-pocket consultation fee for administration of the PPV23 pneumococcal vaccine. If a similar policy decision were made with respect to inclusion of the HZ vaccine in the adult programme, application of a consultation fee could contribute to economic discrimination, as non-card holder individuals with lower income may find it challenging to afford these additional costs. This disparity may disproportionately affect marginalised communities, exacerbating existing economic inequalities. Also, if this technology is not implemented into the immunisation programme, the current significant expense of private HZ vaccination poses a barrier for many individuals. This also presents an ethical issue for a GP or pharmacist who may feel an individual would benefit from vaccination, but they are reluctant to recommend it due to cost barriers.

It is important that the HSE continues to work with GPs, pharmacies, and the public to ensure that those who are eligible and consent to vaccination receive it, and that any barriers to access for disadvantaged groups are identified and minimised. Members of the Irish Traveller community are less likely to access health services, including immunisation.[369] Therefore, methods to increase uptake in this vulnerable group could be considered where necessary, such as the involvement of community healthcare workers from that community to provide peer-to-peer education and encouragement on health-related matters. Vaccination programmes in Ireland generally require specific identification in the form of a PPS number, and undocumented migrants may lack the necessary documents. This can result in exclusion from vaccination services, creating a barrier for those without formal identification. However, exceptions to this rule have been made in the COVID-19 vaccination programme, in exceptional circumstance.[329]

8.5.1 Impact of the technology affecting the distribution of healthcare resources

On the basis of the economic evaluation presented in Chapter 6, vaccinating adults in the general population in Ireland over the age 50 years against HZ is not deemed cost effective. The addition of HZ vaccination to the programme is also associated with a substantial budget impact. Given the constraints of a finite healthcare budget with limited resources, extending the adult immunisation programme to include the HZ vaccine at the modelled cost would pose ethical issues arising from the displacement of existing healthcare. That is, diverting resources to HZ vaccination may entail the curtailment of other services.

The adult HZ immunisation programme is a two-dose regime which will require two GP or pharmacy visits. The number of visits would be markedly higher than the number of visits generated through HZ infection alone (see Chapter 3). While immunisation visits are likely to be medically straightforward, a visit for the diagnosis and treatment of HZ could be more complex and demanding, requiring a significantly longer appointment time. It should be noted that demand for primary care services is high, and it may be considered challenging in some practices to accommodate an additional immunisation visit.

A reduction in HZ infection would lead to a reduction in associated hospitalisation, currently estimated at an average 285 admissions per annum (see Chapter 3). So while vaccination could lead to an initial increase in demand for healthcare resources, they are focused on prevention and would, in turn, lead to a reduced need for treatment. HZ vaccination would result in a shift in demand from a secondary to primary care setting. The other advantage is that unlike care for individuals who are symptomatic as a result of infection, vaccination appointments can be scheduled to improve efficiency and make better use of healthcare resources, such as the organisation of scheduled vaccination clinics.

The introduction of an HZ immunisation programme would have upfront costs in the form of vaccine acquisition. The vaccines must be paid for upfront, while the full advantages in the form of decreased healthcare utilisation for HZ infection would be evident over an extended period. Those healthcare resources could be used elsewhere in the system, potentially with more immediate benefits in terms of reduced ill-health and healthcare utilisation.

8.6 Legislation

In the context of legislation, the introduction of HZ vaccination could have implications that impact basic human rights. These effects can be observed in several ways including the right to health, which emphasises the right of individuals to the highest attainable standard of health. The introduction of HZ vaccination could be seen as a positive step in promoting public health and aligning with the right to health. However, disparities in access, affordability or discriminatory practices could adversely impact this right. If there are barriers in access to HZ vaccination based on factors such as economic status or immigration status, it may constitute a violation of the right to non-discrimination. In Ireland, there is presently no requirement for mandatory adult vaccinations, and the introduction of HZ vaccination is unlikely to influence a change of policy in that regard.

8.7 Ethical consequences of HTA

8.7.1 Choice of outcomes

The effectiveness of HZ vaccination was considered in terms of protection against infection and reductions in HZ-associated complications and hospitalisations. Regarding immunocompetent or general population adults and immunocompromised adults, NIAC:

- recommends the immunisation of all adults aged 65 years and over with RZV.
- recommends immunising hematopoietic stem cell transplant (HSCT) recipients aged 18 and older with RZV.
- suggests considering RZV immunisation for individuals aged 18-49 with compromised immune systems, such as solid organ transplant recipients, those with haematological malignancies, and individuals with advanced or untreated HIV (CD4 count <200 cells/µl).
- recommends the immunisation of adults with immunocompromising conditions aged 50 years and over with RZV.

NIAC notes that these recommendations should be carried out in collaboration with individuals' respective healthcare specialists.[8] The choice of the specific age group or patient group to which the HZ vaccine will be administered on the immunisation programme could potentially exclude other cohorts that may also benefit from vaccination. If vaccination is rolled out to a younger cohort, excluding an older cohort that is at a higher risk of complications may raise concerns about equity and fairness. Access to healthcare interventions, especially preventive measures like vaccination, should be distributed fairly among those who stand to benefit the most. In this context, consideration would need to be given to a catch-up programme for the prevalent population that remains at increased risk (for example, vaccination of older adults if a decision is taken to implement a programme for those aged 50 or 60 years).

From an economic modelling perspective, the impact of HZ immunisation programme is summarised by translating disease states into changes in quality of life. The use of quality-adjusted life-years to capture health benefits enables calculation of an incremental cost-effectiveness ratio (ICER) that is directly comparable with those estimated in other evaluations and against a reference willingness-to-pay threshold.

8.7.2 Timing of assessment

The evidence identified in Chapter 4 on the efficacy, effectiveness and safety of HZ vaccination was collected at a specific point in time and the conclusions could change over time. Waning immunity is a concern, as detailed in Chapter 4. RCT data showed RZV vaccine efficacy wanes by approximately 25% over the first 10

years[197] while a real-world effectiveness study showed RZV wanes 6% over the first four years, albeit noting that these observational data also suggested lower initial effectiveness.[247] Due to this waning immunity, there are ethical considerations in prioritising the older cohort, which are typically more susceptible to severe complications and hospitalisations due to HZ. Further studies may alter our understanding of the rate of waning immunity and whether the rate varies by age, which could impact on estimates of cost effectiveness.

This HTA was conducted on the efficacy, effectiveness and safety of the RZV vaccine Shingrix®, as of February 2024. This is currently the only vaccine on the market if an HZ vaccination programme is implemented, and this presents ethical considerations. The primary concern revolves around the potential lack of competition and choice for recipients, limiting their autonomy in vaccine selection. However, it is important to note that individuals are typically not afforded a choice in regarding any of the vaccines included on the immunisation programme. Future decisions could be impacted by the availability of other vaccines. Ethical considerations also need to be given to the availability of the HZ vaccine. Vaccine shortages are possible, particularly when introducing a new vaccination to the programme and generating heightened interest. Ensuring equitable access to the HZ vaccine is paramount. Ethical distribution should prioritise populations at higher risk of complications or severe outcomes, fostering fairness and justice in vaccine allocation. Due to RZV supply issues in the UK in 2022, RZV was given only to those who were clinically contraindicated for the live vaccine due to their immunocompromised status in order to have sufficient supply for those who needed to receive it.[370] As there is only one RZV vaccine on the market at this time, there are ethical concerns surrounding the pricing and affordability of the vaccine, especially when a single company has a monopoly. Ensuring fair pricing that allows for widespread access without imposing financial burdens on the healthcare system or individuals is crucial. Ethical practices should involve transparent negotiations between the manufacturing company and governmental health agencies. Clear communication about pricing structures, production costs, and any potential conflicts of interest is essential to maintain public trust.

In 2023, HIQA conducted an HTA on the expansion of the childhood immunisation schedule to include varicella vaccination. As of March 2024, the decision to add varicella vaccination has been approved by the Department of Health subject to funding being made available. If varicella vaccination is introduced in Ireland, it carries the potential to change the landscape of HZ disease prevention in the years to come. Looking ahead, if a varicella vaccination programme is successful in preventing primary VZV infection, it should contribute to a decline in HZ cases in the vaccinated cohort. Consideration should be given to understanding the interplay

between varicella vaccination and the epidemiology of HZ which will be crucial for optimising public health strategies and potentially mitigating the need for specific HZ vaccinations in the future.

Evidence availability

RZV vaccination was introduced in the USA for those aged 50 years and older in 2017 and for those at increased risk of HZ in 2021. RZV has been licenced in Europe since 2018. There is 10-year follow-on data from the two pivotal clinical trials reporting efficacy and safety of RZV.[197] A systematic review was conducted on the efficacy, effectiveness and safety of RZV in Chapter 4. There is currently no long-term real-world effectiveness on waning data beyond four years. Individuals should be provided with transparent and accurate information about the limited long-term effectiveness data during the informed consent process. This will ensure that individuals understand the uncertainties surrounding the duration of protection offered by the vaccine. Continuous evaluation of the vaccine's performance over time is essential to gather long-term effectiveness data and inform any necessary adjustments to the vaccination strategies implemented.

8.7.3 Data sources and economic model assumptions

As with any economic modelling exercise, the certainty of the results is limited by the underlying assumptions that underpin the model structure, the availability of data to populate the model and the chosen parameter values. A number of the parameters in the economic model were subject to uncertainty. The reliance on sentinel surveillance data for HZ may underestimate the true disease incidence due to underreporting, potentially skewing the results and leading to an underestimation of the population affected.

There was difficultly in quantifying the burden of disease, especially within immunocompromised populations. There was considerable uncertainty with respect to utility values used in the model. The review of original studies that elicited health-state utility values or disutilities for HZ and PHN disease states identified substantial heterogeneity across studies, which may impact the overall assessment of health outcomes.

Our assumption of homogeneity within Ireland overlooks regional disparities, particularly in rural areas where access to healthcare services, including vaccination programmes, may be limited. There were challenges in identifying certain demographic groups, particularly immunocompromised individuals. This bias could disproportionately affect these populations by inadequately capturing the benefits of vaccination stemming from an underestimation of their numbers. Additionally, the budget-impact analysis within specific subgroups of immunocompromised individuals

neglects the broader population, potentially biasing the results against adequately reflecting the benefits of vaccination for the entire population.

From an ethical perspective, the concern would be that the model structure or the limitations of the available data may result in conclusions that may unfairly disadvantage a particular population group. In this assessment, for example, the lack of data in relation to subgroups of immunocompromised individuals meant that it was not feasible to undertake a cost-utility analysis for those subgroups. Uncertainty in relation to parameters was extensively explored through sensitivity analyses, which shows that the findings were robust to choices of values. Similarly, scenario analysis was undertaken to determine indicative cost-utility results for immunocompromised individuals.

8.8 Discussion

This chapter considered the ethical issues that might arise with the expansion of the adult immunisation programme to include HZ vaccination. In terms of the benefit-harm balance, consideration would need to be given to the potential for the benefits of an HZ immunisation programme to be outweighed by its associated harms. There is clear and consistent evidence that vaccination is very effective at reducing the incidence of HZ. The RZV vaccine contributes to an improved overall quality of life by preventing the pain, discomfort, and potential complications associated with HZ. The evidence suggests that RZV vaccination is safe. While mild local and systemic reactions, such as pain at injection site, fatigue and myalgia, are common, serious adverse events are rare. It is important to note that the benefits of HZ vaccination typically outweigh the potential harms for the majority of individuals, especially for those at higher risk of developing HZ or its complications.

Ethical concerns regarding HZ vaccination also centre on the potential impacts on the current adult immunisation programme. The finite nature of the healthcare budget means that integrating HZ vaccination into the adult immunisation programme would necessitate either reallocating existing resources or securing additional funding. This has the potential to impact the provision of other healthcare technologies within the system. Decisions pertaining to healthcare resource allocation must prioritise fairness, ensuring equitable distribution and consider the opportunity cost of introducing new investments. This may prove difficult as there may be many competing claims requiring prioritisation of care. Ethical issues that may inform such decisions include issues of justice and equity with respect to a fair distribution of benefits and burdens. The results of the economic evaluation showed that vaccinating adults in the general population over the age 50 years against HZ is not cost effective. The associated budget impact is also substantial. In the context of a finite healthcare budget with limited resources, extending the adult immunisation

programme to include the HZ vaccine at the modelled cost would give rise to ethical issues arising from the displacement of existing healthcare services.

In terms of respect for autonomy, autonomy is maintained when individuals have access to clear and comprehensive information concerning the vaccine, including the implications of both receiving and abstaining from it, along with understanding the risks associated with the condition the vaccine aims to prevent. Autonomy also extends to healthcare professionals, it involves the ability to efficiently integrate vaccination activities into daily workflows without compromising the quality of care provided. From the perspective of justice and equity, a decision to add the HZ vaccine to the adult immunisation programme could improve equity of access. Currently, the HZ vaccine is available privately in Ireland, potentially leading to economic discrimination and limiting access for those with lower incomes. The choice of the specific age group or patient group the HZ vaccine will be administered on the immunisation programme could potentially exclude other cohorts that may also benefit from vaccination. If vaccination is rolled out to a younger cohort, there might be concerns about fairness and equity, as an older cohort with a higher risk of complications could be excluded. Access to healthcare interventions, particularly preventive measures like vaccination, should be equitable among those who can derive the greatest benefits.

The timing of the assessment impacts on the available data to evaluate the long-term clinical effectiveness of HZ vaccination. At present, only one real-world study has been published on long-term effectiveness of RZV, which reported that RZV immunity wanes from 79% to 73% over four years.[247] Individuals should be provided with transparent and accurate information about the limited long-term effectiveness data during the informed consent process. Finally, many of the ethical concerns discussed, such as issues of privacy and informed consent, are not unique to HZ vaccination; they also extend to other vaccines included in the national adult immunisation programme.

9 Discussion

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the most efficient use of resources in the healthcare system. The aim of this HTA was to establish the clinical and economic impact of expanding the adult immunisation programme in Ireland to include herpes zoster (shingles) vaccination.

Primary infection with the varicella zoster virus (VZV) results in varicella, commonly known as chickenpox. The virus remains latent in the body's nervous system and can reactivate after a period of time, up to several decades later, resulting in herpes zoster (HZ), also known as shingles. There are two vaccines licensed in Europe for the prevention of HZ and its most common complication, post-herpetic neuralgia (PHN), in adults aged 50 years and older: a live attenuated vaccine (ZVL) and a recombinant adjuvanted vaccine (RZV). RZV is also approved for use in adults aged 18 years and older at increased risk of HZ. The manufacturer of ZVL has highlighted the intention to voluntarily discontinue its manufacture, and so the focus of this HTA was RZV. While some countries have rolled out HZ vaccination programmes based on positive cost-effectiveness analyses, it is noted that the willingness-to-pay threshold and the vaccine price modelled varied. Several countries have evaluated the potential of introducing an HZ vaccination programme and found that it would not be cost effective at the price listed by the manufacturer.[268, 270]

9.1 Burden of disease

Reactivation of the virus as HZ occurs in approximately 30% of people with a history of varicella, with HZ more common with increasing age. Most consultations for HZ occur in a primary care setting, although some people may manage their symptoms alone without visiting a healthcare practitioner. According to international evidence, the risk of HZ increases with age after 50 years of age, and is higher among individuals who are immunocompromised due to immunosuppressive conditions or therapies.

The Irish data available on HZ at a primary care level are based on Health Protection Surveillance Centre (HPSC) data from a network of sentinel general practices. HZ episodes in primary care increase with age. From 2013 to 2022, episode rates for HZ in Ireland were highest in individuals aged 75 to 79 years old (826 per 100,000 population). While the sentinel practice data are nationally representative, they do not describe disease treatment or outcomes. While these data may underestimate total incidence, they are likely broadly representative of the burden of HZ on primary care.

Another source of data available on HZ in Ireland is the Hospital In-Patient Enquiry (HIPE) system, which records inpatient and day-case activity in Irish public acute hospitals. Between 2013 and 2022, the overall mean annual number of patient hospitalisations with a primary diagnosis of HZ was 285, with almost 75% of cases occurring in people aged over 50 years. The number of hospitalisations was highest for those 84 years and older, and the average length of hospital stay for this group was 14.9 days. Between 2013 and 2022, there were 54 deaths in acute hospitals where the person had a primary diagnosis of HZ. The majority (85%) of deaths were in those aged 75 years and older, and almost half (46%) of all deaths occurred in those aged 84 years and older. These figures do not include individuals who may have died in the community as a result of HZ. While these data provided useful information on the typical length of stay and associated healthcare costs of admissions with varicella or herpes zoster, there was limited scope for exploring severe and longer-term complications resulting from infection. Furthermore, it is not known what proportion of the hospitalised cases and deaths occurred in individuals who were immunocompromised due to immunosuppressive conditions or therapies. As HZ is not a notifiable disease, there is no database tracking HZ deaths in the community.

While HZ is typically a self-limiting disease that does not require antiviral treatment in the general population under 50, it can cause severe complications, particularly in those who are immunocompromised. Oral antiviral treatment is recommended within 72 hours of rash onset in all patients over the age of 50 years, to reduce the risk of post-herpetic neuralgia (PHN), with this window increased to one week in certain individuals including those at risk of severe disease. The most frequent complication of HZ is PHN, referring to the persistence of chronic pain after the resolution of the acute rash. For those aged 80 years and over, there is a one-in-five chance of developing PHN as a result of HZ. Those who experience PHN can suffer long term, with between 4 and 25% still experiencing severe pain at nine months.

Varicella vaccination has been examined as part of separate HTA by HIQA.[13] If varicella vaccination is added to the childhood immunisation programme, it would be several decades before an impact would be seen on HZ rates; therefore, the impact of varicella vaccination on HZ rates was not considered in this HTA.

9.2 Clinical effectiveness and safety

Observational and cohort studies were included in a systematic review of clinical efficacy, effectiveness and safety. Overall, data were included from 20 RCTs (47,000 individuals), 12 observational cohort studies (47 million individuals), seven single-arm trials (10,000 individuals) and 11 single-arm observational studies (546,000 individuals), all of which related to Shingrix®, which is the only RZV vaccine licensed

in Europe at the time of writing. There is clear and consistent evidence that RZV vaccination is effective at reducing the incidence of HZ. RCT evidence showed RZV is highly efficacious (92%) at preventing HZ. Effectiveness data (real-world evidence) also showed the vaccine to be effective (70%) at preventing HZ, but the magnitude of effect is lower. The vaccine was also found to be effective in those considered at increased risk of HZ — for example, those with immunocompromising conditions. However, efficacy may be slightly lower in these populations than the general adult population aged over 50 years. Due to limited data and the inconsistency of the available evidence, it is difficult to determine if RZV vaccination prevents HZ-associated complications in individuals who develop HZ despite vaccination. The systematic review also considered evidence in relation to health-related quality of life. The available evidence was found to be limited for individuals who develop HZ after vaccination. However, there was evidence of a reduction in the severity of illness, burden of illness and the duration of clinically significant pain. In terms of safety, the systematic review showed that local adverse events were very common affecting at least 74% of vaccine recipients compared with up to 11.9% of placebo recipients. Systemic reactions were also common. Reactions were generally transient and mild to moderate in intensity. The most frequent reactions reported were pain at the reaction site, fatigue and myalgia. The incidence of potential immune-mediated diseases, serious adverse events (SAEs) and all-cause fatalities were similar in vaccine and placebo groups.

The goal of non-seasonal immunisation programmes is to provide long-term, if not lifetime, protection from a disease. RZV is a relatively new vaccine, first authorised by the European Medicines Agency in 2018; therefore, long-term efficacy and effectiveness data are lacking. The long-term follow-up of two RCTs showed vaccine efficacy waned by about 25% over the first 10 years in the general population aged 50 years and older,[197] while follow-up data from an observational study suggested waning of 6% over the first four years following vaccination, albeit acknowledging that this was in the context of a lower initial reported effectiveness and with limited duration follow-up.[247] Determining the optimum age for vaccination would need to take into account the risk of HZ, risk of complications, waning immunity, and likely remaining years of life.

No data on the long-term vaccine efficacy for those considered at greater risk of HZ were identified. However, waning efficacy is likely to have a considerable impact on this group who could be eligible for vaccination from age 18 years and given evidence that the level of initial protection is lower. The need for booster doses following the primary vaccination schedule has not as yet been established.

There is considerable disparity in vaccine efficacy as reported by RCTs compared with 'real-world' observational studies. Efficacy estimates are considerably higher in RCTs. While RCTs may apply stricter case identification criteria, 'real-world' observational studies may give a better indication of the effectiveness likely to be seen in a national vaccination programme as HZ cases will not typically be laboratory confirmed. Secondary analyses, including investigation of complications of HZ, and subgroup analyses by age were limited by small sample size, leading to inconclusive results.

Evidence on safety suggests that most people who receive RZV can expect to experience a local or systemic adverse event, although the adverse event is unlikely to be serious. Concomitant administration with another vaccine is likely to lead to increased local or systemic adverse events, so this may have implications for programme planning. For example, international data suggest that future uptake of influenza vaccination may be negatively affected by its concomitant administration with RZV, possibly due to individuals attributing any adverse events experienced to the seasonal vaccine. Current immunisation schedules in Ireland allow for the co-administration of the seasonal influenza and COVID-19 booster vaccines. While typically not serious, given the potential for increased local and systemic adverse events, consideration would need to be given to the advantage of concomitant administration with a third vaccine relative to the risk of a reductions in future uptake of the seasonal vaccines.

The overall quality of RCTs, as judged by the ROB2 tool, was deemed at low risk of bias in half of trials. Overall quality of observational trials, as assessed using the ROBINS-I tool, was moderate risk of bias with one study at serious risk of bias. A limitation of the quality appraisal for the included literature in the systematic review is the use of three different tools for quality appraisal which are not comparable. Caution must be employed in comparing outcomes from RCTs, observational and single-arm studies as flaws inherent to their designs affects the certainty of the evidence reported.

9.3 Economic analysis

Results from the de novo economic analysis by HIQA indicate that overall incidence of HZ disease is expected to fall after the introduction of HZ vaccination for adults. Over the 50-year time horizon of the model, vaccination at 60 or 65 years of age with 50% coverage resulted in the largest predicted percentage fall (11.5%) in the total number of HZ cases, relative to no vaccination. This was followed by vaccination at 70 years of age which resulted in a predicted fall of 10.5% in the total number of HZ cases. Due to waning immunity and the increased risk of HZ with age, the reduction in HZ cases was greatest in the 20 years following vaccination. Due to

the reduced risk of PHN following HZ vaccination, the predicted reduction in cases of PHN was greater the earlier vaccination was given. The estimated reduction in cases of PHN varied from 33.5% with vaccination at 50 years of age to 6.5% with vaccination at 85 years old.

In terms of cost effectiveness from the payer perspective (i.e., the HSE), none of the vaccination strategies for the general adult population were estimated to be cost effective, relative to no vaccination, or the previous least costly strategy at a WTP threshold of €45,000 per QALY. The incremental cost-effectiveness ratios ranged from €127,824 per QALY with vaccination at 80 years old to €979,815 per QALY with vaccination at 50 years old. In the base-case analysis (with 50% coverage), the five-year incremental budget impact of an HZ vaccination programme for adults in the general population ranged from €15.1 million with vaccination at 85 years old to €76.8 million with vaccination at 50 years old. The cost of vaccine procurement and administration comprised the majority (94%) of the budget impact associated with the introduction of an HZ vaccination programme. The predicted reduction in HZ cases and the associated fall in the number of hospitalised cases contributed to limited cost savings.

Based on 100% coverage, the five-year incremental budget for all eligible immunocompromised individuals was estimated at €56.2 million. The figure comprised €46.3 million for the cohort aged 50 years and over with non-specific immunocompromising conditions, €6.3 million for those with haematological malignancies, €2.2 million for solid organ transplant recipients, €745,000 for HSCT recipients and approximately €630,000 for the cohort with advanced/untreated HIV. There is considerable uncertainty relating to the number of persons with non-specific immunocompromising conditions who may be eligible for HZ vaccination.

Based on the economic evaluation of HZ vaccination presented, the current evidence suggests that HZ vaccination does not represent an efficient use of healthcare resources. Although the vaccine has been demonstrated to be effective, there is also evidence of waning immunity. Additionally, while resource use associated with HZ and PHN in primary care is not insignificant, hospitalisation rates for HZ are low. When these costs and outcomes associated with HZ are modelled and vaccination is introduced, the results suggest that at the base-case vaccine price (€151) used in the model, HZ vaccination is not an efficient use of resources. The base-case results of the economic evaluation were robust to various sensitivity and scenario analyses. However, a threshold analysis identified that an 80% drop in the vaccine price, to €30.00 per dose, would result in the cost-effectiveness ratios for those vaccinated at 65, 70, 75, 80 and 85 years of age falling below €45,000 per QALY. While the cost of the vaccine used in this assessment was based on the current price, the potential to

negotiate substantial discounts may be limited by the fact that supply is limited to a single market authorisation holder.

9.4 Organisational issues

If a decision were made to fund HZ vaccination as part of the adult immunisation programme, there would be significant financial and logistical implications depending on the population group for whom the vaccine is funded. Specifically, if vaccination were to be extended to all individuals included in the NIAC recommendations, a staggered roll-out approach would likely be required, both to ensure adequate capacity within primary care services to facilitate vaccination of large numbers of individuals and to manage vaccine supply.

In countries such as the USA and Australia, providers have noted initial high demand for RZV, which outweighed supply. Recent information campaigns have meant that many Irish people are aware of HZ and its associated complications. Therefore, if a vaccine were to be made available, there could be strong demand at the launch of the programme. If demand for RZV were to exceed supply, consideration would need to be given to defining priority groups for vaccination. Accordingly, an information campaign would be required to clearly indicate who is eligible for the vaccine and how to avail of it through the adult immunisation programme. There may be challenges in identifying subgroups of adults aged 18 years and older that may be eligible on the basis of an identified immunocompromising condition. Consideration would therefore need to be given to engagement with clinical specialists in tertiary services to support uptake in these subgroups.

As outlined in Chapter 4, HIQA identified seven new vaccine compounds which are being evaluated in clinical trials. If these trials are successful, these candidate vaccines could become alternatives to RZV, alleviating potential supply issues and creating opportunities for price negotiations. The candidate vaccines are in early phase (phase 1 and 2) clinical trials.

As identified in section 9.2, co-administration of the HZ vaccine with other vaccines in the adult immunisation programme is possible. Co-administration would potentially reduce the overall number of vaccine-related healthcare visits, potentially reducing the burden on patients and healthcare providers. However, it would likely still necessitate an additional visit given that RZV is a two-dose vaccine, with both doses required to be administered within a six-month window, per the licensed indications. As noted in section 9.2, there is a potential that co-administration could impact the future uptake of the seasonal vaccines given the increased frequency of adverse events with vaccine co-administration. It is also noted that given the two-

dose schedule for RZV, consideration may be needed around measures to track and contact people, in order to support uptake of the second dose.

9.5 Ethical and social considerations

In terms of the benefit-harm balance, the benefits of HZ vaccination typically outweigh the potential harms for the majority of individuals, especially for those at higher risk of developing HZ or its complications.

Evidence from this HTA highlights that, based on current data, vaccinating adults in the general population over the age of 50 years against HZ is not cost effective and is associated with a substantial budget impact. The healthcare budget is finite; including HZ vaccination in the adult immunisation programme could require reallocation of resources, potentially impacting the existing healthcare system by diverting resources from other more cost-effective interventions or from the overall healthcare fund. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity costs (the value of the next best alternative forgone) of new investments are considered. This may prove difficult as there may be many competing claims requiring prioritisation of care. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens.

The timing of the assessment impacts on the available data to evaluate the long-term clinical effectiveness of HZ vaccination, with a maximum published follow-up data of four years and ten years in observational and RCT studies, respectively. Individuals should be provided with transparent and accurate information about the limited long-term effectiveness data during the informed consent process. Many of the ethical concerns discussed, such as issues of privacy and informed consent, are not unique to HZ vaccination; they also extend to other vaccines included in the national adult immunisation programme.

9.6 Conclusion

In excess of 90% of the population contract varicella and are therefore susceptible to reactivation of the virus as herpes zoster. Approximately 30% of people who have had varicella will go on to have HZ.

The most frequent complication of HZ is post-herpetic neuralgia (PHN), referring to persistent chronic pain after the resolution of the acute rash. PHN can significantly alter individuals' lives, inflicting debilitating pain, disrupting daily activities, sleep, and emotional well-being. The probability of PHN increases with age, increasing from a one in 10 chance in 50- to 59-year-olds to one in five in those aged over 80 years.

Both the risk of HZ and complications from HZ increase with age after 50 years and among individuals who are immunocompromised due to immunosuppressive conditions or therapies.

There is clear and consistent evidence that the recombinant adjuvanted vaccine (RZV) vaccine is safe and effective at reducing HZ cases, but effectiveness diminishes over time. While associated adverse events are typically not severe, most people who are vaccinated will experience minor local or systemic adverse events.

As most people have a short-course of symptoms, and will not be hospitalised, the economic impact of treating HZ is not substantial. At the submitted price, the current evidence suggests that HZ vaccination does not represent an efficient use of healthcare resources. The results of economic evaluation show that an RZV vaccination programme would fall well outside typically accepted willingness-to-pay thresholds. The findings of the cost-effectiveness analysis for the general adult population were robust to sensitivity and scenario analyses. While those with immunocompromising conditions are more likely to develop HZ, and therefore are more likely to benefit from vaccination, the question of cost effectiveness of vaccination of this group could not be addressed due to limited data availability. Considering a vaccine uptake of 50%, the five-year incremental budget impact of a HZ vaccination programme for adults as they turn 65 years old (no catch-up for older adults) would be €53.3 million. For all adults aged 65 years and older would be €218 million. The five-year incremental budget for eligible immunocompromised persons (with 100% coverage), was estimated at €56.4 million.

A decision to fund the RZV vaccine as part of the adult programme could have significant financial and logistical implications depending on the population groups for whom the vaccine is funded. Funding interventions, which have been found to be not cost effective, could create issues of justice and equity with respect to a fair distribution of benefits and burdens.

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Appendix A Chapter 4: Clinical efficacy, effectiveness and safety

Appendix A.1 Search strategies

Sources searched

Databases	Number of results	Date searched
Medline Complete via EBSCOhost	999	10/07/2023
Embase via Elsevier	1433	10/07/2023
The Cochrane Library via Wiley	559	10/07/2023
CINAHL via EBSCOhost	282	10/07/2023
ClinicalTrials.gov	219	10/07/2023
Total	3492	
Total after duplicates removed in Endnote and Covidence	**2164**	

Search strategies

Database Name	Medline Complete via Ebscohost
Date search was run	10/07/23

#	Query	Limiters/Expanders	Last Run Via	Results
S19 combines concepts 1, 2 and 3				
S19	S14 AND S18	Limiters - Date of Publication: 20080101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	999

Concept 3 study design filters designed by Health Library Ireland (HSE) Librarians for Systematic Reviews, RCTs and cohort studies

S18	S15 OR S16 OR S17	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	4,418,412
S17	MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH "Follow Up Studies" OR MH "Retrospective Studies" OR MH "Case Control Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up" OR retrospective OR "case control" OR "case referent" OR "case comparison") N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up" OR retrospective OR "case control" OR "case referent" OR "case comparison") N1 (study OR analys* OR design OR method*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	2,588,781

S16	MH "Randomized Controlled Trial" OR PT "Randomized Controlled Trial" OR TI random* N2 trial OR AB random* N2 trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	983,639
S15	MH "Systematic Review" OR MH "Meta Analysis" OR PT "MetaAnalysis" OR TI systematic* N1 (review* OR overview*) OR AB systematic* N1 (review* OR overview*) OR TI "meta analys*" OR TI "meta analyz*" OR AB "meta analys*" OR AB "meta analyz* OR TI literature N2 (review* OR overview*) OR AB literature	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,384,848
S14	S6 AND S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	5,489

Concept 2 Vaccination

S13	S7 OR S8 OR S9 OR S10 OR S11 OR S12	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	850,924

			Database - MEDLINE Complete	
S12	AB ((zoster OR shingles) N3 vaccin*) OR TI ((zoster OR shingles) N3 vaccin*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,975
S11	TI Shingrix OR AB Shingrix	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	97
S10	AB (vaccin* OR inoculat* OR immuni*) OR TI (vaccin* OR inoculat* OR immuni*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	792,794
S9	(MH "Herpes Zoster Vaccine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen -	1,117

			Advanced Search Database - MEDLINE Complete	
S8	(MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	208,975
S7	(MH "Vaccination+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	109,230
Concept 1 Herpes zoster				
S6	S1 OR S2 OR S3 OR S4 OR S5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	24,425

S5	AB varicella N3 virus* OR TI varicella N3 virus*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	9,655
S4	AB "herpes zoster" OR TI "herpes zoster"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	10,927
S3	AB shingles OR TI shingles	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,643
S2	(MH "Herpesvirus 3, Human")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database -	8,059

			MEDLINE Complete	
S1	(MH "Herpes Zoster+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	13,227

Database Name	Embase via Ovid
Date search was run	10/07/23

Database(s): **Embase** 1974 to 2023 July 07
Search Strategy:

#	Searches	Results
1	exp herpes zoster/	30384
2	shingles.ab,ti.	2376
3	"herpes zoster".ab,ti.	14920
4	(varicella adj3 virus*).ab,ti.	12205
5	1 or 2 or 3 or 4	39302
6	exp vaccination/	242758
7	exp immunization/	373753
8	exp varicella zoster vaccine/	4332
9	(vaccin* or inoculat* or immuni*).ab,ti.	930266
10	Shingrix.ab,ti.	157
11	((zoster or shingles) adj3 vaccin*).ab,ti.	2627
12	6 or 7 or 8 or 9 or 10 or 11	1005797

13	5 and 12	8871
14	exp Systematic Review/ or exp Meta Analysis/ or ((systematic* adj2 (review* or overview*)) or (meta analys* or meta analyz*) or (literature adj3 (review* or overview*))).ti,ab.	1067415
15	exp Randomized Controlled Trial/ or randomized controlled trial.pt. or ((random* adj3 trial) or (placebo* or single blind* or double blind* or triple blind*)).ti,ab.	1148810
16	exp Cohort Analysis/ or exp Longitudinal Study/ or exp Prospective Study/ or exp Follow Up/ or exp Retrospective Study/ or exp Case Control Study/ or ((cohort or longitudinal or prospective or follow up or retrospective or case control or case referent or case comparison) adj2 (study or analys* or design or method*)).ti,ab.	4908184
17	14 or 15 or 16	6563741
18	13 and 17	2475
19	limit 18 to yr="2008 -Current"	2230
20	limit 19 to embase	1433

Database Name	The Cochrane Library
Date search was run	10/07/23

ID Search Hits

#1 MeSH descriptor: [Herpes Zoster] explode all trees 826

#2 MeSH descriptor: [Herpesvirus 3, Human] explode all trees 179

#3 (shingles):ti,ab,kw (Word variations have been searched) 183

#4 ("herpes zoster"):ti,ab,kw (Word variations have been searched) 2553

#5 (varicella NEAR/3 virus*):ti,ab,kw (Word variations have been searched) 507

#6 #1 OR #2 OR #3 OR #4 OR #5 2804

#7 MeSH descriptor: [Vaccination] explode all trees 4014

#8 MeSH descriptor: [Immunization] explode all trees 6911

#9 MeSH descriptor: [Herpes Zoster Vaccine] explode all trees 110

#10 (vaccin* OR inoculat* OR immuni*):ti,ab,kw (Word variations have been searched) 40949

#11	(Shingrix):ti,ab,kw (Word variations have been searched)	22
#12	((zoster OR shingles) NEAR/3 vaccin*):ti,ab,kw (Word variations have been searched)	391
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	41104
#14	#6 and #13 with Cochrane Library publication date from Jan 2008 to present	559

Database Name	CINAHL via EBSCOhost
Date search was run	10/07/23

#	Query	Limiters/Expanders	Last Run Via	Results
S21	S12 AND S20	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	282
S20	S17 OR S18 OR S19	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	1,318,076
S19	MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research	815,401

	"Follow Up Studies" OR MH "Retrospective Studies" OR MH "Case Control Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up" OR retrospective OR "case control" OR "case referent" OR "case comparison") N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up" OR retrospective OR "case control" OR "case referent" OR "case comparison") N1 (study OR analys* OR design OR method*)	Search modes - Boolean/Phrase	Databases Search Screen - Advanced Search Database - CINAHL Complete	
S18	MH "Randomized Controlled Trial" OR PT "Randomized Controlled Trial" OR TI random* N2 trial OR AB random* N2 trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	328,295
S17	S13 OR S14 OR S15 OR S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	316,365
S16	OR AB systematic* N1 (review* OR overview*) OR TI "meta analys*" OR TI "meta analyz*" OR AB "meta analys*" OR AB "meta analyz* OR TI literature N2 (review* OR	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen -	256,547

	overview*) OR AB literature N2 (review* OR overview*)		Advanced Search Database - CINAHL Complete	
S15	PT systematic review	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	143,879
S14	(MH "Meta Analysis")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	69,785
S13	(MH "Systematic Review")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	121,939
S12	S6 AND S12	Limiters - Published Date: 20080101- Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases	1,365

		Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL Complete	
S11	S7 OR S8 OR S9 OR S10	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Database - CINAHL Complete	105,172
S10	AB ((zoster OR shingles) N3 vaccin*) OR TI ((zoster OR shingles) N3 vaccin*)	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Database - CINAHL Complete	865
S9	TI Shingrix OR AB Shingrix	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Database - CINAHL Complete	50

S8	AB (vaccin* OR inoculat* OR immuni*) OR TI (vaccin* OR inoculat* OR immuni*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	96,443
S7	(MH "Herpes Zoster Vaccine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	631
S6	(MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	32,989
S5	S1 OR S2 OR S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database -	5,386

			CINAHL Complete	
S4	AB varicella N3 virus* OR TI varicella N3 virus*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	1,504
S3	AB "herpes zoster" OR TI "herpes zoster"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	2,523
S2	AB shingles OR TI shingles	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	865
S1	(MH "Herpes Zoster+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	3,630

Search Database - CINAHL Complete

Database Name	INAHTA https://database.inahta.org/
Date search was run	10/07/23
How the results were selected	Used the Advanced Search screen to find relevant results
Search Strategies	Search 1: Search 2:

Database Name	ClinicalTrials.gov
Date search was run	10/07/23
Search Strategies	Search 1: vaccination | Shingles Search 2: Shingrix Search 3: "herpes zoster vaccine" | Adult, Older Adult

Appendix A.2 Additional data extraction

Table A 1 Vaccine efficacy in general population aged ≥50 years against herpes zoster in different cohorts

Study author, year	Age	Follow up	Incidence rate of HZ (per 1,000 person-years)		Efficacy % (95% CI)
			RZV (n/py)	Placebo (n/py)	
(ZOE-pIMD) Dagnew, 2021[222]	≥50y	4.4y	1.1 (4/3,611.70)	11.1 (38/3,408.80)	90.5 (73.5-97.5)
	50-59y		1.1 (1/885.60)	14.2 (11/775.60)	92.8 (50.5-99.8)
	60-69y		0 (0/638.30)	13.6 (8/588.80)	100 (54.9-100)
	70-79y		1.2 (2/1,623.00)	7.9 (13/1,647.30)	84.4 (30.8-98.3)
	≥80y		2.2 (1/464.80)	15.1 (6/397.00)	86.2 (-13.5-99.7)
(ZOE-underlying conditions)† Oostvogels, 2019[240]	1 medical condition	NR	0.4 (5/12,269.20)	8.9 (109/12,213.40)	95.4 (89.0–98.5)
	2 medical conditions		0.6 (7/11,797.10)	8.3 (97/11,746.40)	92.8 (84.7–97.2)
	3 medical conditions		0.9 (8/8,803.70)	9.6 (88/9,162.60)	90.5 (80.5–96.0)
	At least 3 medical conditions		1 (19/19,417.00)	10.3 (199/19,338.40)	90.5 (84.8–94.4)
	At least 4 medical conditions		1 (11/10613.30)	10.9 (111/10175.80)	90.6 (82.4–95.4
	At least 5 medical conditions		1 (5/5132.50)	11 (52/4742.40)	91.2 (78.0–97.3
	At least 6 medical conditions		1 (2/2039.20)	10.5 (20/1910.10)	90.9 (62.5–99.0)
(ZOE-Frailty)	Non-frail	4y	0.4 (8/21803.00)	8.8 (188/21443.00)	95.8 (91.6-98.2)

Study author, year	Age	Follow up	Incidence rate of HZ (per 1,000 person-years)		Efficacy % (95% CI)
			RZV (n/py)	Placebo (n/py)	
Curran, 2021[239]	Pre-frail		0.8 (18/21842.00)	8.6 (191/22250.00)	90.4 (84.4-94.4)
	Frail		1 (5/5158.00)	9.9 (46/4663.00)	90.2 (75.4-97.0)
	Unknown		0 (0/186.00)	25.8 (5/194.00)	100.0 (14.6-100.0)

Key: CI – confidence interval; HZ – herpes zoster; n – number of herpes zoster cases; py – person years; RZV – recombinant zoster vaccine; y – years
Note: † Underlying medical conditions included: hypertension, osteoarthritis and/or vertebral disorders, dyslipidaemia, diabetes, osteoporosis/osteopenia, gastroesophageal reflux disease, sleep disorder, prostatic diseases, hypothyroidism, depression, coronary heart disease, cataract, asthma, respiratory disorders, renal disorders.

Table A 2 Estimated EQ-5D scores for utility loss during the acute HZ period in the placebo group

Study author, year	Age	Timepoint	Estimated utility	Estimated utility loss
ZOE-Quality of life Curran, 2019b[241]	ZOE-50: 50-59y	Pre HZ	0.880	
		Day 0	0.622	0.258 (0.204-0.313)
		Week 1	0.685	0.195 (0.136-0.254)
		Week 2	0.736	0.145 (0.081-0.208)
		Week 3	0.821	0.059 (-0.007-0.125)
		Week 4	0.872	0.008 (-0.060-0.076)
	ZOE-50: 60-69y	Pre HZ	0.879	
		Day 0	0.637	0.242 (0.176-0.308)
		Week 1	0.713	0.166 (0.102-0.230)
		Week 2	0.791	0.087 (0.020-0.155)
		Week 3	0.800	0.078 (0.008-0.150)
		Week 4	0.799	0.080 (0.007-0.152)
	ZOE-50: ≥70y	Pre HZ	0.800	
		Day 0	0.517	0.284 (0.209-0.358)
		Week 1	0.610	0.190 (0.110-0.270)

Study author, year	Age	Timepoint	Estimated utility	Estimated utility loss
		Week 2	0.703	0.097 (0.011-0.184)
		Week 3	0.713	0.087 (0.000-0.175)
		Week 4	0.765	0.035 (-0.054-0.124)
	Combined ZOE-70: 70-79y	Pre HZ	0.840	
		Day 0	0.606	0.234 (0.191-0.277)
		Week 1	0.674	0.166 (0.121-0.210)
		Week 2	0.686	0.153 (0.107-0.200)
		Week 3	0.735	0.105 (0.057-0.152)
		Week 4	0.787	0.052 (0.004-0.100)
	Combined ZOE-70: ≥80y	Pre HZ	0.753	
		Day 0	0.542	0.211 (0.133-0.289)
		Week 1	0.645	0.108 (0.030-0.187)
		Week 2	0.686	0.067 (-0.017-0.150)
		Week 3	0.682	0.071 (-0.015-0.157)
		Week 4	0.749	0.004 (-0.083-0.091)

Table A 3 Estimated EQ-5D scores for utility loss in autologous HSCT recipients during the acute HZ period in the placebo group

Study author, year	Age	Time Point	Estimated utility	Estimated utility loss
ZOE-HSCT Curran, 2019a[207]	ZOE-HSCT: 18-49y	Pre HZ	0.8523	
		Day 0	0.5188	0.3335
		Week 1	0.5316	0.3206
		Week 2	0.6716	0.1807

Study author, year	Age	Time Point	Estimated utility	Estimated utility loss
		Week 3	0.7607	0.0916
		Week 4	0.7796	0.0727
	ZOE-HSCT: ≥50y	Pre HZ	0.8003	
		Day 0	0.5969	0.2308
		Week 1	0.5797	0.2206
		Week 2	0.6856	0.1147
		Week 3	0.6696	0.1307
		Week 4	0.7359	0.0644

Table A 4 Vaccine reactogenicity in general population aged ≥50 years against herpes zoster in different cohorts

Study author, year	Follow up	Condition	Local/injection site reactions %				Systemic reactions %			
			Any local event		Grade 3 local event		Any systemic event		Grade 3 systemic event	
			RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	Placebo
(ZOE-pIMD) Dagnew, 2021[222]	4.4y	Pre-existing pIMD	NR	NR	NR	NR	NR	NR	NR	NR
(ZOE-Frailty) Curran, 2021[239]	4y	Non-frail	84.7	11.2	9.5	0.2	68.2	27.4	12.0	1.8
		Pre-frail	78.9	11.6	8.7	0.3	63.0	29.3	9.4	2.0
		Frail	68.5	3.2	10.2	1.1	50.8	32.9	10.2	4.7

Study author, year	Follow up	Condition	Local/injection site reactions %				Systemic reactions %			
			Any local event		Grade 3 local event		Any systemic event		Grade 3 systemic event	
			RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	Placebo
		Unknown	81.0	11.8	4.8	0	52.4	33.3	0	0
(ZOE-underlying conditions)† Oostvogels, 2019[240]	NR	1 medical condition	NR	NR	NR	NR	NR	NR	NR	NR
		2 medical conditions	NR	NR	NR	NR	NR	NR	NR	NR
		3 medical conditions	NR	NR	NR	NR	NR	NR	NR	NR
		≥3 medical conditions	NR	NR	NR	NR	NR	NR	NR	NR
		≥4 medical conditions	NR	NR	NR	NR	NR	NR	NR	NR
		≥5 medical conditions	NR	NR	NR	NR	NR	NR	NR	NR
		≥6 medical conditions	NR	NR	NR	NR	NR	NR	NR	NR

Key: CI – confidence interval; HZ – herpes zoster; n – number of herpes zoster cases; py – person years; RZV – recombinant zoster vaccine; y – years; NR – not reported
Note: † Underlying medical conditions included: hypertension, osteoarthritis and/or vertebral disorders, dyslipidaemia, diabetes, osteoporosis/osteopenia, gastroesophageal reflux disease, sleep disorder, prostatic diseases, hypothyroidism, depression, coronary heart disease, cataract, asthma, respiratory disorders, renal disorders.

Table A 5 Vaccine safety in general population aged ≥50 years against herpes zoster in different cohorts

Author, year	Follow up	Condition	Any AE %		Grade 3 AEs %		SAEs %		pIMDs %		All-cause death %	
			RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	ZVL	RZV	Placebo
(ZOE-pIMD)	4.4y	Pre-existing pIMD	NR	NR	NR	NR	14.6	11.7	NR	NR	5.1	6.6

Author, year	Follow up	Condition	Any AE %		Grade 3 AEs %		SAEs %		pIMDs %		All-cause death %	
			RZV	Placebo	RZV	Placebo	RZV	Placebo	RZV	ZVL	RZV	Placebo
Dagnew, 2021[222]												
(ZOE-Frailty) Curran, 2021[239]	4y	Non-frail	87.3	32.2	17.4	1.8	6.2	5.7	1.3	1.2	2.1 0*	1.9 0*
		Pre-frail	83.4	33.7	14.1	2.2	11.5	12.1	1.3	1.4	4.9 0*	5.5 0*
		Frail	73.6	36.1	15.3	5.1	18.6	22.7	1.0	1.8	11.1 0*	12.4 0*
		Unknown	85.7	41.2	4.8	0	NR	NR	NR	NR	NR	NR
(ZOE-underlying conditions)† Oostvogels, 2019[240]	NR	1 medical condition	NR	NR	NR	NR	6.9	7.7	1.4	1.2	3.2	3.4
		2 medical conditions	NR	NR	NR	NR	9.7	9.7	1.3	1.6	3.9	4.5
		3 medical conditions	NR	NR	NR	NR	12	13	1.2	1.2	5.6	5.8
		≥3 medical conditions	NR	NR	NR	NR	14.7	14.8	1.2	1.5	6.4	6.7
		≥4 medical conditions	NR	NR	NR	NR	16.9	16.4	1.2	1.7	7.1	7.4
		≥5 medical conditions	NR	NR	NR	NR	19.8	21	1.1	1.6	8.6	9.5
		≥6 medical conditions	NR	NR	NR	NR	21.5	25.2	1.2	1.4	10.2	11.3

Key: AE – adverse event; CI – confidence interval; HZ – herpes zoster; n – number of herpes zoster cases; py – person years; RZV – recombinant zoster vaccine; SAE – serious adverse event; y – Years; NR – not reported

Note: †Underlying medical conditions included: hypertension, osteoarthritis and/or vertebral disorders, dyslipidaemia, diabetes, osteoporosis/osteopenia, gastroesophageal reflux disease, sleep disorder, prostatic diseases, hypothyroidism, depression, coronary heart disease, cataract, asthma, respiratory disorders, renal disorders.

*denotes number related to vaccination

Table A 6 Ongoing clinical trials

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT05596526 (MSHINGVAX)	University Hospital, Geneva	RVZ	Multiple Sclerosis Patients	ongoing	Phase 2	Nov-2024
NCT05775718	University of Colorado	RZV	Allogeneic Transplants	ongoing	Phase 2	Dec-2030
NCT04128189	University of Colorado	RZV	Renal transplant recipients	ongoing	Phase 3	Jan-2024
NCT03798691	University of Wisconsin	RZV	Inflammatory Bowel Disease Patients Treated With Vedolizumab	ongoing	Phase 4	Feb-2024
NCT05898464	Seoul National University Hospital	RZV	HIV	ongoing	Phase 4	Mar-2026
NCT05580458	National Institute of Allergy and Infectious Disease	RZV	HIV	ongoing	Phase 1 and 2 studies	Oct-2027

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT03591770	Boston Medical Center	UC therapies and Shingrix	Ulcerative colitis patients on tofacitinib monotherapy in comparison to other therapies	ongoing	Phase 4	Dec-2024
NCT05575830	Calmy Alexandra, University Hospital, Geneva	RZV	Healthy controls and HIV patients	ongoing	Phase 4	Sep-2025
NCT04869982 Zoster-076	GSK	RZV	Chinese adults aged 50 years	Ongoing	Phase 4	Jul-2023
NCT05879419	University of Sao Paulo General Hospital	RZV	Autoimmune rheumatic disease	Ongoing	Phase 4	May-2027
NCT04516408	Renji Hospital	RZV	Systemic lupus erythematosus	Ongoing	RCT - Phase reported as not applicable	Sep-2023
NCT05304351	Curevo Inc	CRV-101 vaccine	Adults 50 years and over	Ongoing	Phase 2	Oct-2029

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT05559671	NYU Langone Health	RZV	Systemic lupus erythematosus	Ongoing	Phase 4	Aug-2026
NCT05856084	MAXVAX Biotechnology LLC	Recombinant vaccine (LZ901)	Healthy Subjects Aged 30 Years and Above	Ongoing	Phase 2	Mar-2026
NCT04748939	Tuen Min Hospital	RZV	Patients 18 years and older with rheumatic diseases undergoing immunosuppressive or biologic/targeted DMARD therapies	Ongoing	Phase 4	Oct-2025
NCT03604406	Oregon Health and Science University	RZV and Zostavax	Rheumatoid Arthritis Patients Using Abatacept	Ongoing	Phase 2	Jun-2024

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT05769049	Jiangsu Rec-Biotechnology Co Ltd	REC610 vs RZV	Two age groups: 40-59 years and 60 years and older	Ongoing	Phase 1	Mar-2024
NCT05636436	MAXVAX Biotechnology LLC	Recombinant vaccine (LZ901)	Healthy adults	Ongoing	Phase 1	Dec-2024
NCT05718037	Wuhan BravoVax Co Ltd	Recombinant vaccine BV211	Healthy adults	Ongoing	Phase 1	Jul-2024
ChiCTR2200055617	Hubei Provincial Center for Disease Control and Prevention	Recombinant vaccine (LZ901)	Healthy adults 50-70 years old	ongoing	Phase 1	unclear
ChiCTR2200058609	Hubei Provincial Center for Disease Control and Prevention	Recombinant vaccine	Healthy adults 50-70 years old	Recruitment Pending completion Phase 1	phase 2	unclear

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
				ChiCTR2200055617		
NCT03993717	Emory University	RZV	Renal transplant recipients	Enrolment and study activities are temporarily suspended due to COVID-19	Phase 4	Dec-2024
NCT04047979	Emory University	RZV	Two groups of participants: those aged 50 to 60 years or those who are 70 years old and above	Completed	estimated completion June 2024 Phase 2 Immunogenicity	Jun-2024
NCT05701800	ModernaTx	mRNA-1468 vs shingrix	Healthy Adults ≥50 Years of Age	ongoing	Phase 1/2	Jul-2024
NCT05371080	GSK	RZV additional doses	Long-term follow-up comparing additional and no additional doses after original trials	ongoing	Phase 3b	Aug-2027

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT04176939 Zoster-073	GSK	RZV	previously vaccinated kidney transplant adults – two additional doses	ongoing	Phase 3	Aug-2024
JPRN-jRCT1031220071	Yoshimura Yukihiro, Yokohama Municipal Children's Hospital	RZV vs Live attenuated vaccine	HIV	ongoing	Reported as not applicable	Dec-2030
NCT05871541	Immorna Biotherapeutics Inc	JCXH-105 vs Shingrix	healthy subjects 50-69 years	ongoing	phase I	Mar-2024
NCT04091451 Zoster-062	GSK	RZV vs placebo	adults who have had a previous episode of HZ	ongoing	Phase 1	Feb-2024
NCT05750017	Beijing Luzhu Biotechnology Co., Ltd.	Recombinant vaccine LZ901	healthy adults 50-70 years	ongoing	Phase 1	Mar-2024

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT05703607	Pfizer	VZV modRNA vs RZV	Healthy adults 50-69 years	ongoing	Phase 1 and Phase 2 substudies	Aug-2030
NCT05811754	GSK	RZV	Pregnancy in immunodeficient or immunosuppressed adult pregnant women between 18 and 49 years of age	ongoing	Observational	Apr-2029
NCT05219253	GSK	RZV	healthy adults aged 50 years and older in India	ongoing	Phase 3	Apr-2023
ISRCTN26495549	University Hospitals Bristol NHS Foundation Trust	multiple vaccines	Co-administration of flu, HZ and COVID-19 vaccines	ongoing	Phase 4	Jan-2025
NCT05554068	Loyola University	RZV	Allogenic HSCT patients	ongoing	Phase 2	Nov-2026

Clinical trial number (other trial name)	Sponsor	Vaccine	Population	Status	Clinical trial phase	Estimated completion of study
NCT05047770	GSK	RZV, Flu D-QIV, mRNA-1273 COVID-19	Healthy adults	Completed not yet published	Phase 3	Note: No publication of RZV + Flu D-QIV to date

Key: DMARD – disease-modifying anti-rheumatic drug; GSK – GlaxoSmithKline; HIV – human immunodeficiency virus; HSCT – hematopoietic stem cell transplantation; HZ – herpes zoster; mRNA – messenger ribonucleic acid; RCT – randomised control trial; RZV – recombinant zoster vaccine; UC – ulcerative colitis; VZV – Varicella Zoster Virus

Figure A 1. Risk of bias (ROB2) for RCTs - traffic-light plot

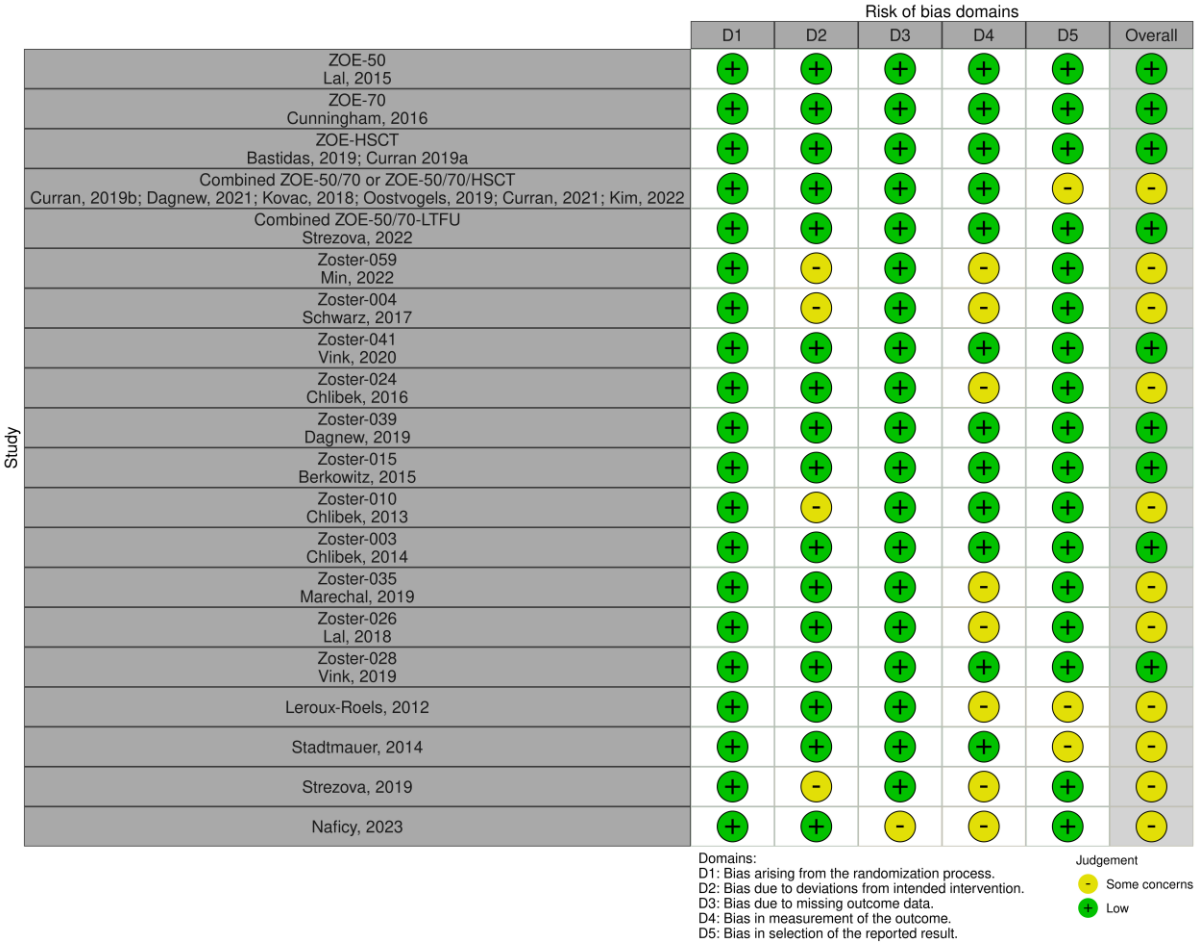
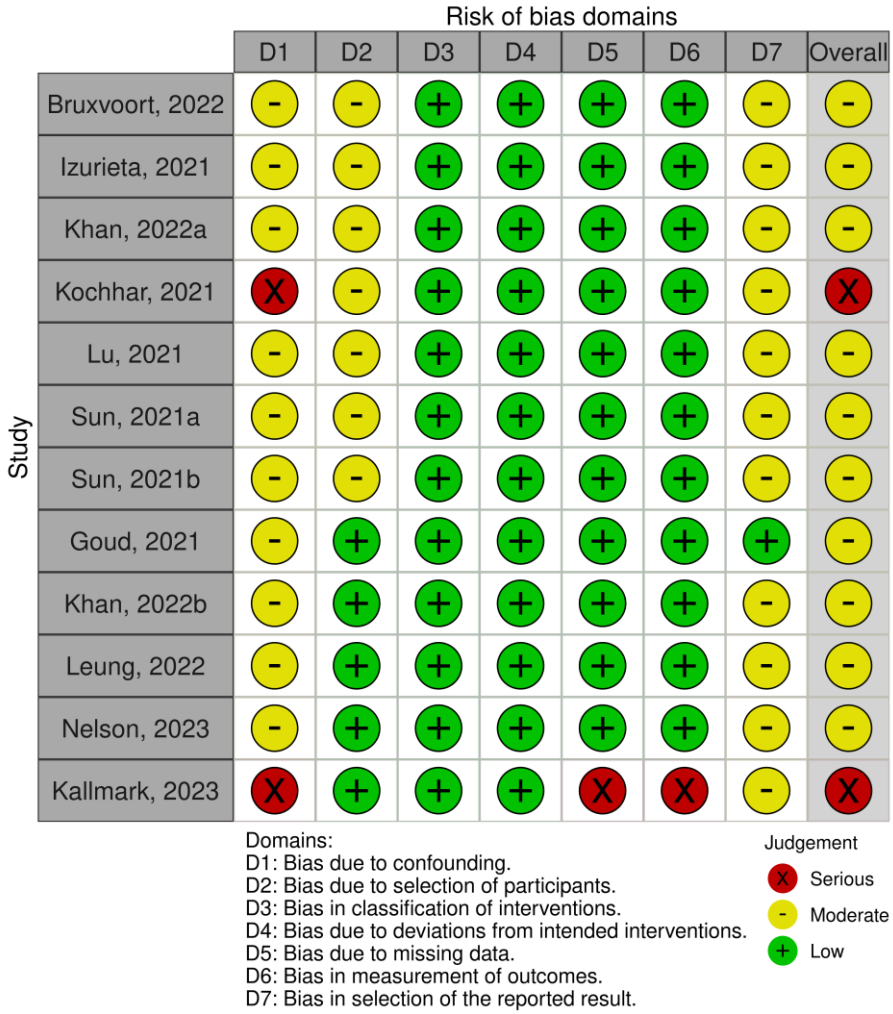


Figure A 2. Risk of bias (ROBINS-I) for non-randomised studies - traffic-light plot



Appendix A.3 Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a. Truly representative (one star)
   b. Somewhat representative (one star)
   c. Selected group
   d. No description of the derivation of the cohort
2) Ascertainment of exposure
   a. Secure record (e.g., surgical record) (one star)
   b. Structured interview (one star)
   c. Written self-report
   d. No description
   e. Other
3) Demonstration that outcome of interest was not present at start of study
   a. Yes (one star)
   b. No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
   a. The study controls for age, sex and marital status (one star)
   b. Study controls for other factors (list)
      _____ (one star)
   c. Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
   a. Independent blind assessment (one star)
   b. Record linkage (one star)
   c. Self-report
   d. No description
   e. Other
2) Was follow-up long enough for outcomes to occur
   a. Yes (one star)

b. No
c. Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts
a. Complete follow up - all subject accounted for (one star)
b. Subjects lost to follow up unlikely to introduce bias - number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
c. Follow-up rate less than 80% and no description of those lost
d. No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix B Chapter 5: Rapid review of methodology for economic modelling studies

Table A 7 Search Strategies

Database Name	Embase (Ovid) 1974 to 2023 June 26
Date search was run	27 June 2023

#	Searches	Results
1	exp herpes zoster/	30332
2	shingles.ab,ti.	2371
3	"herpes zoster".ab,ti.	14902
4	(varicella adj3 virus*).ab,ti.	12194
5	1 or 2 or 3 or 4	39243
6	exp vaccination/	241937
7	exp immunization/	372773
8	exp varicella zoster vaccine/	4321
9	(vaccin* or inoculat* or immuni*).ab,ti.	928530
10	Zostavax.ab,ti.	274
11	Shingrix.ab,ti.	157
12	((zoster or shingles) adj3 vaccin*).ab,ti.	2624
13	6 or 7 or 8 or 9 or 10 or 11 or 12	1003846
14	5 and 13	8854
15	Economics/	244381
16	Cost/	62659
17	exp Health Economics/	1029608
18	Budget/	33897
19	budget*.ti,ab,kf.	48088
20	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	350993
21	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	536817
22	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	294438
23	(value adj2 (money or monetary)).ti,ab,kf.	4126
24	Statistical Model/	173460
25	economic model*.ab,kf.	6326
26	Probability/	150468
27	markov.ti,ab,kf.	38726

28	monte carlo method/	51057
29	monte carlo.ti,ab,kf.	63958
30	Decision Theory/	1851
31	Decision Tree/	21822
32	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	52362
33	or/15-32	2016378
34	14 and 33	1248
35	limit 34 to yr="2018 - Current"	496

Database Name	Medline (EBSCO)
Date search was run	27 June 2023

#	Query	Limiters/Expanders	Results
S17	S15 AND S16	Limiters - Date of Publication: 20180101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	338
S16	MH "Economics" OR MH "Models, Economic" OR MH "Costs and Cost Analysis+" OR MH "Economic Aspects of Illness" OR MH "Resource Allocation+" OR MH "Economic Value of Life" OR MH "Economics, Pharmaceutical" OR MH "Economics, Dental" OR MH "Fees and Charges+" OR MH "Budgets" OR MH "Decision Trees" OR TI budget* OR TI (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco-economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR TI (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR TI (value N2 (money OR monetary)) OR TI (markov OR monte carlo) OR TI (decision* N2 (tree* OR analy* OR model*)) OR AB budget* OR AB (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR AB (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR AB (value N2 (money OR monetary)) OR AB (markov OR monte carlo) OR AB (decision* N2 (tree* OR analy* OR model*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,938,496
S15	S6 AND S14	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,479
S14	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	849,254
S13	AB ((zoster OR shingles) N3 vaccin*) OR TI ((zoster OR shingles) N3 vaccin*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,968
S12	TI Shingrix OR AB Shingrix	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	97

S11	TI Zostavax OR AB Zostavax	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	164
S10	AB (vaccin* OR inoculat* OR immuni*) OR TI (vaccin* OR inoculat* OR immuni*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	791,164
S9	(MH "Herpes Zoster Vaccine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,114
S8	(MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	208,765
S7	(MH "Vaccination+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	109,064
S6	S1 OR S2 OR S3 OR S4 OR S5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	24,396
S5	AB varicella N3 virus* OR TI varicella N3 virus*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9,645
S4	AB "herpes zoster" OR TI "herpes zoster"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	10,907
S3	AB shingles OR TI shingles	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,641
S2	(MH "Herpesvirus 3, Human")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	8,053
S1	(MH "Herpes Zoster+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	13,219

Database Name		CINAHL(EBSCO)		
Date search was run		27 June 2023		
#	**Query**	**Limiters/Expanders**	**Last Run Via**	**Results**

S14	S5 AND S12 AND S13	Limiters - Published Date: 20180101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	71
S13	MH "Economics" OR MH "Costs and Cost Analysis+" OR MH "Economic Aspects of Illness" OR MH "Resource Allocation+" OR MH "Economic Value of Life" OR MH "Economics, Pharmaceutical" OR MH "Economics, Dental" OR MH "Fees and Charges+" OR MH "Budgets" OR MH "Decision Trees" OR TI budget* OR TI (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco-economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR TI (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR TI (value N2 (money OR monetary)) OR TI (markov OR monte carlo) OR TI (decision* N2 (tree* OR analy* OR model*)) OR AB budget* OR AB (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR "pharmaco-economic*" OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed) OR AB (cost* N2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)) OR AB (value N2 (money OR monetary)) OR AB (markov OR monte carlo) OR AB (decision* N2 (tree* OR analy* OR model*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	461,840
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	105,082
S11	AB ((zoster OR shingles) N3 vaccin*) OR TI ((zoster OR shingles) N3 vaccin*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	865
S10	TI Shingrix OR AB Shingrix	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	50
S9	TI Zostavax OR AB Zostavax	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	82
S8	AB (vaccin* OR inoculat* OR immuni*) OR TI (vaccin* OR inoculat* OR immuni*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	96,346

S7	(MH "Herpes Zoster Vaccine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	629
S6	(MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	33,013
S5	S1 OR S2 OR S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	5,376
S4	AB varicella N3 virus* OR TI varicella N3 virus*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	1,502
S3	AB "herpes zoster" OR TI "herpes zoster"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	2,516
S2	AB shingles OR TI shingles	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	865
S1	(MH "Herpes Zoster+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	3,628

Table A 8 Excluded studies

Title	Authors	Published Year	DOI	Exclusion reason
Clinical and economic implications of increasing access to herpes zoster vaccination rate in community pharmacies	Watanabe, A. H.; Veettil, S. K.; Le, L. M.; Bald, E.; Tak, C.; Chaiyakunapruk, N.	2023	https://dx.doi.org/10.1016/j.japh.2023.05.012	Wrong comparator
Cost-effectiveness analysis of vaccination with recombinant zoster vaccine among hematopoietic cell transplant recipients and persons with other immunocompromising conditions aged 19 to 49 years	Leidner, A. J.; Anderson, T. C.; Hong, K.; Ortega-Sanchez, I. R.; Guo, A.; Pike, J.; Prosser, L. A.; Dooling, K. L.	2023	https://dx.doi.org/10.1016/j.jval.2022.08.003	Wrong patient population
Cost-effectiveness of recombinant zoster vaccine for adults aged ≥50 years in China	Jiang, Minghuan; Yao, Xuelin; Peng, Jin; Feng, Liuxin; Ma, Yue; Shi, Xinke; Fang, Yu; Fang, Hai	2023	10.1016/j.amepre.2023.05.007	Not a high income country
How large could the public health impact of introducing recombinant zoster vaccination for people aged ≥50 years in five Latin American countries be?	Han, R.; Gomez, J. A.; de Veras, B.; Pinto, T.; Guzman-Holst, A.; Nieto, J.; van Oorschot, D. A. M.	2023	https://dx.doi.org/10.1080/21645515.2022.2164144	Wrong study design
Cost-effectiveness of the recombinant zoster vaccine (RZV) against herpes zoster: An updated critical review	Giannelos, N.; Ng, C.; Curran, D.	2023	https://dx.doi.org/10.1080/21645515.2023.2168952	Wrong study design
Public health impact of recombinant zoster vaccine for prevention of herpes zoster in US adults immunocompromised due to cancer	Curran, D.; Patterson, B. J.; Carrico, J.; Salem, A.; La, E. M.; Lorenc, S.; Hicks, K. A.; Poston, S.; Carpenter, C. F.	2023	https://dx.doi.org/10.1080/21645515.2023.2167907	Wrong study design
Cost-effectiveness of an adjuvanted recombinant zoster vaccine in adults with inflammatory bowel disease	Caldera, Freddy; Spaulding, Aaron C.; Borah, Bijan; Moriarty, Jim; Zhu, Ye; Hayney, Mary S.; Farraye, Francis A.	2023	10.1111/apt.17454	Wrong patient population
Return on Investment (ROI) of three vaccination programmes in Italy: hpv at 12 years, herpes zoster in adults, and influenza in the elderly	Barbieri, M.; Boccalini, S.	2023	https://dx.doi.org/10.3390/vaccines11050924	Wrong outcomes
EE396 Public health impact and cost-effectiveness of herpes zoster vaccination for older adults in the Netherlands	Van der Pol, S.; Giannelos, N.; Joost, S.; Wilschut, J. C.; Postma, M. J.; Boersma, C.	2022	https://dx.doi.org/10.1016/j.jval.2022.09.642	Abstract only
Incremental net monetary benefit of herpes zoster vaccination: a systematic review and meta-analysis of cost-effectiveness evidence	Udayachalerm, Sariya; Renouard, Maranda G.; Anothaisintawee, Thunyarat; Thakkinstian, Ammarin; Veettil, Sajesh K.; Chaiyakunapruk, Nathorn	2022	10.1080/13696998.2021.2008195	Wrong study design
The impact of increased recombinant zoster vaccine use on the burden of herpes zoster among adults aged 50 to 59 years	Singer, D.; Salem, A.; Stempniewicz, N.; Ma, S.; Poston, S.; Curran, D.	2022	https://dx.doi.org/10.1093/ofid/ofac492.1199	Abstract only
Modeling the impact of exogenous boosting and universal varicella vaccination on the clinical and economic burden of varicella and herpes zoster in a dynamic population for England and Wales	Sharomi, O.; Xausa, I.; Nachbar, R.; Pillsbury, M.; Matthews, I.; Petigara, T.; Elbasha, E.; Pawaskar, M.	2022	https://dx.doi.org/10.3390/vaccines10091416	Wrong intervention

Title	Authors	Published Year	DOI	Exclusion reason
EE526 Public health impact and cost-effectiveness of recombinant zoster vaccine for vaccinating immunocompromised adults against herpes zoster in the United States	Salem, A.; Curran, D.; Carrico, J.; La, E. M.; Lorenc, S.; Hicks, K.; Poston, S.; Carpenter, C. F.	2022	https://dx.doi.org/10.1016/j.jval.2022.09.767	Wrong patient population
Recombinant Zoster Vaccine for High-Risk Ageing Adults in the Netherlands: Cost-Effectiveness and Value of Information Analyses	Pham, T. H.; Van der Schans, J.	2022	https://dx.doi.org/10.1016/j.jval.2022.09.309	Wrong patient population
EE265 Health, Productivity and Budget Impact of Vaccinating 50-64 Year Old Employees in Austria Against Herpes Zoster With Recombinant Zoster Vaccine	Nishimwe, M. L.; Uhl, G.	2022	https://dx.doi.org/10.1016/j.jval.2022.09.513	Wrong study design
Cost-Effectiveness Analysis of Vaccinating Against Herpes Zoster With Adjuvanted Recombinant Zoster Vaccine in Switzerland	Nishimwe, M. L.; Fischer, L.; Kientsch, U.; Giannelos, N.	2022	https://dx.doi.org/10.1016/j.jval.2022.09.346	Abstract only
Cost-effectiveness of herpes zoster vaccines in the U.S.: A systematic review	Meredith, Neil R.; Armstrong, Edward P.	2022	10.1016/j.pmedr.2022.101923	Wrong study design
EE202 Estimating the Public Health Benefits of Preventing Herpes Zoster and Postherpetic Neuralgia in Greece by Zoster Vaccines: A Modelling Study	Kotsopoulos, N.; Gargalianos, P.; Giannelos, N.; Nishimwe, M. L.; Papagiannopoulou, V.; Rallis, D.; Lenas, E.; Vernadakis, E.; Stratigos, A.	2022	https://dx.doi.org/10.1016/j.jval.2022.09.452	Abstract only
EE388 Public Health and Economic Implications of Increasing Access to Herpes Zoster Vaccination Rate in Community Pharmacies	Hikiji Watanabe, A.; Veettil, S. K.; Le, L.; Tak, C.; Bald, E.; Chaiyakunapruk, N.	2022	https://dx.doi.org/10.1016/j.jval.2022.04.636	Abstract only
Vaccination for quality of life: herpes-zoster vaccines	Lang, Pierre-Olivier; Aspinall, Richard	2021	10.1007/s40520-019-01374-5	Wrong study design
Modelling a cost-effective vaccination strategy for the prevention of varicella and herpes zoster infection: A systematic review	Hodgkinson, B.; Wang, T.; Byrnes, J.; Scuffham, P.	2021	https://dx.doi.org/10.1016/j.vaccine.2021.01.061	Wrong study design
Long-term efficacy data for the recombinant zoster vaccine: Impact on public health and cost effectiveness in Germany	Curran, D.; Van Oorschot, D.; Matthews, S.; Hain, J.; Salem, A.; Schwarz, M.	2021	https://dx.doi.org/10.1007/s41999-021-00585-2	Abstract only
Cost-Effectiveness of Recombinant Zoster Vaccine for Vaccinating Immunocompromised Adults Against Herpes Zoster in the United States	Curran, D.; Salem, A.; Lorenc, S.; Patterson, B.; Carrico, J.; Hicks, K. A.; La, E. M.; Poston, S.; Carpenter, C. F.	2021	https://dx.doi.org/10.1093/ofid/ofab466.222	Wrong patient population
Cost-effectiveness analysis of recombinant zoster vaccine for the prevention of herpes zoster in immunocompromised adults diagnosed with select cancers in the United States	Curran, D.; Patterson, B.; Carrico, J.; Salem, A.; La, E.; Lorenc, S.; Hicks, K.; Poston, S.; Carpenter, C.	2021	https://dx.doi.org/10.1002/ajh.26351	Wrong patient population
Cost-effectiveness of a comprehensive immunization program serving high-risk, uninsured adults	Wilson, K. J.; Brown, H. S.; Patel, U.; Tucker, D.; Becker, K.	2020	https://dx.doi.org/10.1016/j.ypmed.2019.105860	Wrong patient population

Title	Authors	Published Year	DOI	Exclusion reason
PIN21 Are WE FULLY Capturing the Social IMPACT of Vaccines?	Silver, M.; Neumann, P. J.; Nyaku, M. K.; Roberts, C. S.; Sinha, A.; Fang, S.; Morais, E.; Ollendorf, D. A.	2020	https://dx.doi.org/10.1016/j.jval.2020.08.862	Wrong study design
Recombinant zoster vaccine administration in an allergy/immunology practice: a medical and economic case	Russell, H. G.; Tankersley, M. S.	2020	https://dx.doi.org/10.1016/j.anai.2020.02.006	Wrong study design
Estimating the fiscal impact of three vaccination strategies in Italy	Ruggeri, Matteo; Di Brino, Eugenio; Cicchetti, Americo	2020	10.1017/S0266462320000069	Wrong study design
Herpes zoster vaccination: Live or inactivated vaccines? or no vaccination at all?	Moussa, M.; Sonnichsen, A.	2020	https://dx.doi.org/10.3238/zfa.2020.0051-0055	Wrong study design
Herpes zoster vaccine for older adults?	Kerst, A. J. F. A.; Stolk, L. M. L.	2020	https://dx.doi.org/10.35351/gebu.2020.9.16	Wrong study design
Aggregate health and economic burden of herpes zoster in the United States: illustrative example of a pain condition	Harvey, M.; Prosser, L. A.; Rose, A. M.; Ortega-Sanchez, I. R.; Harpaz, R.	2020	https://dx.doi.org/10.1097/j.pain.0000000000001718	Wrong study design
Herpes zoster in people who are immunocompromised: what are the options for prevention?	Warren-Gash, C.; Breuer, J.	2019	https://dx.doi.org/10.1016/S1473-3099%2819%2930399-8	Wrong study design
PMU14 Cost-benefit analysis of vaccination against four preventable diseases in older adults in the united states	Talbird, S.; La, E.; Carrico, J.; Poston, S.; Poirrier, J. E.; DeMartino, J. K.; Hogea, C.	2019	https://dx.doi.org/10.1016/j.jval.2019.04.1177	Abstract only
Cost-effectiveness of herpes zoster vaccination	Sriwijitalai, W.; Wiwanitkit, V.	2019	https://dx.doi.org/10.4103/ijpvm.IJPVM_291_19	Wrong study design
Prevention of shingles: Better protection and better value with recombinant vaccine	Shafran, S. D.	2019	https://dx.doi.org/10.7326/M19-0141	Wrong study design
Public health and economic impact of adjuvanted recombinant zoster vaccine adoption for a large, integrated delivery network: utilizing real-world epidemiological data in a budget impact model	Patterson, B.; Herring, W.; Van Oorschot, D.; Curran, D.; Carico, J.; Zhang, Y.; Ackerson, B.; Bruxvoort, K.; Sy, L.; Tseng, H.	2019	https://dx.doi.org/10.18553/jmcp.2019.25.10-a.s1	Abstract only
Cost-effectiveness of adult vaccinations: A systematic review	Leidner, A. J.; Murthy, N.; Chesson, H. W.; Biggerstaff, M.; Stoecker, C.; Harris, A. M.; Acosta, A.; Dooling, K.; Bridges, C. B.	2019	https://dx.doi.org/10.1016/j.vaccine.2018.11.056	Wrong study design
Herpes Zoster Vaccine in Older Adults With Inflammatory Bowel Disease	Lai, S. W.	2019	https://dx.doi.org/10.1016/j.cgh.2019.04.076	Wrong study design
Cost-effectiveness of an adjuvanted recombinant zoster vaccine in older adults in the United States who have been previously vaccinated with zoster vaccine live	Curran, Desmond; Patterson, Brandon J.; Van Oorschot, Desiree; Buck, Philip O.; Carrico, Justin; Hicks, Katherine A.; Lee, Bruce; Yawn, Barbara P.	2019	10.1080/21645515.2018.1558689	Wrong patient population
Cost-Effectiveness of Herpes Zoster Vaccination: A Systematic Review	Chiyaka, Edward T.; Nghiem, Van T.; Zhang, Lu; Deshpande, Abhishek; Mullen, Patricia Dolan; Le, Phuc	2019	10.1007/s40273-018-0735-1	Wrong study design

Title	Authors	Published Year	DOI	Exclusion reason
THE potential public health impact of herpes zoster vaccination in the 65 years of age cohort in Italy	Antonio, V.; Boccalini, S.; Dari, S.; Clarke, C.; Curran, D.; Loiacono, I.; Pitrelli, A.; Puggina, A.; Tosatto, R.; Van Oorschot, D.; Franco, E.	2019	https://dx.doi.org/10.1080/21645515.2019.1657753	Wrong outcomes
Efficacy, Cost-Effectiveness of Herpes Zoster Vaccination		2019		No article identified
COST-effectiveness of varicella and herpes zoster vaccination in the Swedish population	Wolff, E.	2018	https://dx.doi.org/10.1016/j.jval.2018.09.1375	Abstract only
Cost-effectiveness of candidate adjuvanted subunit vaccine for vaccinating U.S. adults not previously vaccinated against Herpes Zoster	Patterson, B.; Curran, D.; Buck, P.; Varghese, L.; Oorschot, D.; Carrico, J.; Hicks, K.; Lee, B.; Yawn, B.	2018		Abstract only
UK experience of herpes zoster vaccination can inform varicella zoster virus policies	Ogunjimi, B.; Beutels, P.	2018	https://dx.doi.org/10.1016/S2468-2667%2817%2930245-1	Wrong study design
Which Herpes Zoster Vaccine is Most Cost-Effective?...JAMA Intern Med 2018;178:248-58	Ngai, Ka Ming Gordon	2018		Wrong study design
Evolution of Herpes Zoster Vaccines and Their Economic Value	Najafzadeh, Mehdi	2018	10.1001/jamainternmed.2017.7442	Wrong study design
Cost-effectiveness of the advisory committee on immunization practices recommendation for a new recombinant zoster vaccine in older adults	Le, P. H.; Rothberg, M. B.	2018		Abstract only
Cost-effectiveness of the Recommendations of the Advisory Committee on Immunization Practices for the Recombinant Adjuvanted Zoster Subunit Vaccine	Le, Phuc; Rothberg, Michael B.	2018	10.1001/jamainternmed.2018.3200	Wrong study design
Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults	Le, P.; Rothberg, M. B.	2018	https://dx.doi.org/10.1001/jamainternmed.2017.7431	Included in earlier systematic review
Determining the optimal strategy for the live-attenuated herpes zoster vaccine in adults	Harvey, M. J.; Denton, B. T.; Prosser, L. A.; Hutton, D. W.	2018	https://dx.doi.org/10.1016/j.vaccine.2018.06.059	Wrong study design
Avoiding rash decisions about zoster vaccination: Insights from cost-effectiveness evidence	Good, C. B.; Parekh, N.; Hernandez, I.	2018	https://dx.doi.org/10.1186/s12916-018-1231-3	Wrong study design
Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine: To the editor	Good, C. B.; Hernandez, I.	2018	https://dx.doi.org/10.1001/jamainternmed.2018.2029	Wrong study design
Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines	Dooling, K. L.; Guo, A.; Patel, M.; Lee, G. M.; Moore, K.; Belongia, E. A.; Harpaz, R.	2018	https://dx.doi.org/10.1111/ajt.14683	Wrong study design
Limited Focus in Evaluation of Vaccine Cost-effectiveness	Curran, D.; Van Oorschot, D.; Buck, P.	2018	https://dx.doi.org/10.1001/jamainternmed.2018.5801	Wrong study design
IS the recombinant zoster vaccine also cost-effective for the German population >=50 years of age?	Anastassopoulou, A.; Van Oorschot, D.; Poulsen Nautrup, B.; Varghese, L.; von	2018	https://dx.doi.org/10.1016/j.jval.2018.09.1372	Abstract only

Title	Authors	Published Year	DOI	Exclusion reason
	Krempelhuber, A.; Neine, M.; Lorenc, S.; Curran, D.			

Table A 9 Data extraction tables

General study characteristics	**Author Name, Year of Publication, DOI**	Carpenter et al. 2019 DOI: 10.1093/ofid/ofz219
	Region, Country	USA
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥50 years (data for men and women modelled together).
	Funding	Not stated
Model characteristics	**Model type**	Four state Markov model with cycle time of 1 year Health states: 1. No HZ 2. HZ 3. Complications of HZ (PHN/HZ ophthalmicus/hospitalisation) 4. Dead
	Model software	Excel
	Perspective	Societal
	Time horizon	Lifetime (data were modelled until last cohort member was assumed to die at age 100 years).
	Comparator	No vaccination and alternative vaccine
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way and two-way) and probabilistic
Intervention strategy	**Vaccine type**	ZVL and RZV
	Dosing schedule	ZVL: 1-dose; RZV: 2-dose
	Age at vaccination	50 years, 60 years and 70 years
	Coverage rate	First dose unclear and assumed that 95.5% returned for second dose of RZV
Model input parameters	**Efficacy/effectiveness**	ZVL 50-59yrs: 69.8%; 60-69yrs: 65.7%; 70-79yrs: 40.7%; 80-100yrs: 15.7% RZV 50-59yrs: 96.9%; 60-69yrs: 94.1%; 70-79yrs: 89.9%; ≥80yrs: 89.7%
	Waning	ZVL 5.44% p.a. RZV 1-dose: 8% p.a.; 2-dose: 5.44% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Direct medical costs - acute HZ - PHN - ocular complications ▪ Vaccination costs - vaccine - vaccine administration - vaccine related serious adverse event **Indirect costs** ▪ Productivity loss - no pain HZ - mild HZ - moderate HZ - severe HZ - mild pain, PHN - moderate pain, PHN - severe pain, PHN
		Measurement and valuation **Direct costs** ▪ Direct medical costs - USD cost per case of acute HZ - USD cost per case of PHN - USD cost per case of ocular complications ▪ Vaccination costs - USD cost per vaccine dose - USD cost per vaccine dose administration - USD cost per vaccine related serious adverse event **Indirect costs** ▪ Productivity loss - number of hours lost per case with no pain HZ - number of hours lost per case with mild HZ - number of hours lost per case with moderate HZ - number of hours lost per case with severe HZ - number of hours lost per case with mild pain, PHN - number of hours lost per case with moderate pain, PHN - number of hours lost per case with severe pain, PHN

			- average hourly wages
	Effects included	**Type of Effects** **Direct effects** ▪ HZ and PHN cases ▪ Complications (assumed to be independent) - PHN - acute ocular involvement - hospitalisation - death **Direct effects of vaccination** ▪ Adverse events due to vaccination - ZVL related injection site reaction - ZVL related serious adverse event - RZV related injection site reaction - RZV related serious adverse event	**Measurement and valuation** **Direct effects** ▪ Reduction in incidence of HZ (by age group) ▪ Probability of ocular complications (by age group) ▪ Probability of PHN (by age group) ▪ Probability of moderate or severe PHN (by age group) ▪ Probability of moderate PHN in individuals with mod-severe PHN (Note: the numbers in Table 1 look incorrect as base case = 0.5 and range is 0.03 to 0.08) ▪ Probability of pain given HZ (by scale of pain) ▪ Incidence of death due to HZ (by age group) **Direct effects of vaccination** ▪ Probability of adverse events due to vaccination **QALYs** ▪ QALY loss per case acute HZ - no pain HZ - mild HZ - moderate HZ - severe HZ - average acute HZ ▪ QALY loss per case PHN (1yr) - mild pain PHN - moderate pain PHN - severe pain PHN ▪ QALY loss per case ocular complications (1yr) ▪ QALY loss per case common adverse reaction per vaccine dose ▪ QALY loss per case serious adverse reaction per vaccine dose
Economic results	**Type of summary ratio**	ICER (Incremental cost/QALY gained)	
	Overall payer perspective result	N/A	
	Overall societal perspective result	For individuals vaccinated at age: ▪ 50 years, ZVL ICER = USD 118,535/QALY gained versus no vaccination ▪ 60 years, ZVL ICER = USD 42,712/QALY gained versus no vaccination ▪ 70 years, ZVL ICER = USD 88,251/QALY gained versus no vaccination ▪ 50 years, RZV ICER = USD 91,156/QALY gained versus no vaccination ▪ 60 years, RZV ICER = USD 19,300/QALY gained versus no vaccination ▪ 70 years, RZV ICER = USD 1,407/QALY gained versus no vaccination ▪ 60 years, RZV dominates ZVL ▪ 70 years, RZV dominates ZVL	
Authors conclusions	Vaccination with RZV was more cost effective (versus no vaccination) than ZVL in all age groups studied. Vaccination with RZV at age 50 years appears cost effective (versus no vaccination), with an ICER <USD 100,000 per QALY gained.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; PHN post-herpetic neuralgia; QALY – quality-adjusted life year; RZV – recombinant zoster vaccine; USA – United States of America; USD – United States dollar; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Carrico et al. 2021 DOI: 10.1016/j.vaccine.2021.07.029 [Relevant data also extracted from Talbird et al. 2021 - DOI: 10.1080/21645515.2020.1780847]
	Region, Country	USA
	Type of Economic Evaluation	CBA
	Population	Immunocompetent adults aged ≥50 years
	Funding	Industry (GlaxoSmithKline Biologicals SA)
Model characteristics	**Model type**	Population-based age-structured Decision Tree 'Infected' pathway alternatives included: 1. complicated (PHN and or non-pain complications) 2. uncomplicated (end-point) 3. non-medically attended (end-point) 'Complicated' pathway alternatives included 1. alive (end-point) 2. dead (end-point)
	Model software	Excel
	Perspective	1. Direct medical 2. Societal
	Time horizon	30 years (base case)
	Comparator	No vaccination
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way)
Intervention strategy	**Vaccine type**	ZVL used exclusively in 2017, followed by exclusive use of RZV from 2018 forward
	Dosing schedule	ZVL: 1-dose and RZV: 2-dose
	Age at vaccination	50 years
	Coverage rate	Current coverage 1st dose 50-59yrs: 0.0%*; 60-64yrs: 23.9%; ≥65yrs: 37.4% 2nd dose 69.0% *Assumed that HZ vaccine coverage for ages 50–59yrs reaches current coverage level of 60- to 64-year-old age group (23.9%) five years after introduction of RZV in year 2 (2018).
Model input parameters	**Efficacy/effectiveness**	ZVL 50-69yrs: 63.9%; ≥70yrs: 30.0% RZV 50-69yrs: 95.8%; ≥70yrs: 89.1%
	Waning	ZVL (duration of protection) 50-69yrs: 12yrs; ≥70yrs: 6yrs RZV (duration of protection) 50-69yrs: 30yrs; ≥70yrs: 20yrs
	Costs included	**Type of cost** **Direct costs** ▪ Direct medical costs - uncomplicated case of HZ - complicated case with PHN or non-pain complications - non-medically attended case - over-the-counter (OTC) medication ▪ Vaccination costs - vaccine - vaccine administration - vaccine-related adverse event **Indirect costs** ▪ Productivity loss
		Measurement and valuation **Direct costs** ▪ Direct medical costs - USD cost per uncomplicated case of HZ - USD cost per complicated case with PHN or non-pain complications - USD cost per non-medically attended case - USD cost for OTC medication per non-medically attended case ▪ Vaccination costs - USD cost per vaccine dose (public and private) - USD cost per vaccine dose administration - USD cost per vaccine-related local adverse event per dose - USD cost per vaccine-related adverse event requiring GP visit - USD cost per vaccine-related adverse event requiring ED visit

		- disease case - disease-related mortality - time for vaccination	- USD cost per vaccine-related adverse event requiring hospitalisation **Indirect costs** ▪ Productivity loss (human capital method) - cost of productivity loss per disease case (by age group) - cost of productivity loss due to mortality from disease case (by age group) based on remaining life expectancy at age of death and discounted lifetime remaining earnings - number of hours lost per due to time for vaccination - cost per hour for time for vaccination
	Effects included	**Type of Effects** **Direct effects** ▪ HZ cases ▪ Uncomplicated case of HZ ▪ Complicated case with PHN or non-pain complications ▪ Non-medically attended case ▪ Disease-related deaths **Direct effects of vaccination** ▪ Vaccine related adverse events	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ (by age group) ▪ Probability of uncomplicated case of HZ (by age group) ▪ Probability of complicated case with PHN or non-pain complications (by age group) ▪ Probability of non-medically attended case (by age group) ▪ Probability of disease-related deaths (by age group) **Direct effects of vaccination** ▪ Probability of local adverse event (by age group) ▪ Probability of GP visit for vaccine related adverse event (by age group) ▪ Probability of ED visit for vaccine related adverse event (by age group) ▪ Probability of hospitalisation for vaccine related adverse event (all ages)
Economic results	**Type of summary ratio** **Overall direct medical cost perspective result** **Overall societal perspective result**	BCR (benefit-cost ratio) 10yr time horizon: BCR = 0.41 versus no vaccination 20yr time horizon: BCR = 0.59 versus no vaccination 30yr time horizon: BCR = 0.66 versus no vaccination 10yr time horizon: BCR = 1.01 versus no vaccination 20yr time horizon: BCR = 1.41 versus no vaccination 30yr time horizon: BCR = 1.57 versus no vaccination	
Authors conclusions	Study results highlight the economic value of vaccination programs for older adults in the US and indicate that efforts to further increase vaccination coverage may be warranted and economically justifiable.		

Key: BCR – benefit-cost ratio; CBA – cost-benefit analysis; ED – emergency department; GP – general practitioner; HZ – herpes zoster; N/A – not applicable; OTC – over-the-counter; PHN – post-herpetic neuralgia; RZV – recombinant zoster vaccine; USD – United States dollar; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Curran et al. 2018 DOI: 10.1016/j.vaccine.2018.07.005
	Region, Country	USA
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥50 years
	Funding	Industry (GlaxoSmithKline Biologicals SA)
Model characteristics	**Model type**	Multi-cohort Markov model (five age groups for people aged ≥50 years [i.e. 50–59, 60–64, 65–69, 70–79, ≥80]) with 1 year cycles (ZONA) Health states: 1. Healthy 2. HZ 3. PHN (from HZ and recurrent HZ) 4. Non PHN complications (from HZ and recurrent HZ) 5. Recovered 6. Recurrent HZ 7. Death from HZ 8. Death from other causes
	Model software	Excel
	Perspective	Societal
	Time horizon	Lifetime
	Comparator	No vaccination and ZVL
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Vaccine type**	RZV
	Dosing schedule	2-dose (two months apart)
	Age at vaccination	≥60 years
	Coverage rate	1st dose: 100% 2nd dose: 69.0%
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose 50-69yrs: 90.1%; ≥70yrs: 69.5% RZV 2-dose 50-69yrs: 98.4%; ≥70yrs: 97.8%
	Waning	RZV 1-dose Years 1-4: 5.4% p.a.; Year 5 onwards: 5.1% p.a. RZV 2-dose Years 1-4: 1% p.a.; Years 5 until age 69yrs: 2.35% p.a.; ≥70yrs: 3.6% p.a. (bootstrap analysis)
	Costs included	**Type of cost** **Direct costs** ▪ Direct medical costs - HZ without PHN - HZ with PHN - ocular complication - neurological complication - cutaneous complication - other non-pain complication ▪ Vaccination costs - vaccine - vaccine administration - vaccine-related local/general adverse event - vaccine-related outpatient visit - vaccine-related emergency room visit
		Measurement and valuation **Direct costs** ▪ Direct medical costs - USD cost per HZ case without PHN (by age group) - USD cost per HZ case with PHN (by age group) - USD cost per ocular complication - USD cost per neurological complication - USD cost per cutaneous complication - USD cost per other non-pain complication ▪ Vaccination costs - USD cost per vaccine dose - USD cost per vaccine dose administration - USD cost per vaccine-related adverse event per dose (by age group) - USD cost per vaccine related local/general adverse event (all

		- vaccine-related hospitalisation **Indirect costs** ▪ Productivity loss - HZ case - vaccine-related adverse event	ages) - USD cost per vaccine related outpatient visit (by age group) - USD cost per vaccine related emergency room visit (by age group) - USD cost per vaccine related hospitalisation (by age group) **Indirect costs** ▪ Productivity loss - cost of productivity loss per HZ case (by age group) based on work hours lost and hourly USD wage estimates - cost of productivity loss per vaccine-related adverse event, based on: o work hours lost for medical attention for vaccine-related adverse event requiring an outpatient visit o work hours lost for medical attention for vaccine-related adverse event requiring an ER visit o work hours lost for medical attention for vaccine-related adverse event requiring a hospital visit o hourly USD wage estimates
Effects included		**Type of Effects** **Direct effects** ▪ HZ ▪ PHN ▪ Recurrent HZ ▪ Recurrent HZ with PHN ▪ Disease-related deaths ▪ Ocular complications ▪ Neurological complications ▪ Cutaneous complications ▪ Other non-pain complications **Direct effects of vaccination** ▪ Vaccine-related local/general adverse events ▪ Vaccine-related outpatient visit ▪ Vaccine-related emergency room visit ▪ Vaccine-related hospitalisation	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ (by age group) ▪ Percentage of HZ cases with PHN (by age group) ▪ Incidence of recurrent HZ (by age group) ▪ Percentage of recurrent HZ cases with PHN (by age group) ▪ Case fatality rate for HZ cases (by age group) ▪ Rate of ocular complications (by age group) ▪ Rate of neurological complications (by age group) ▪ Rate of cutaneous complications (by age group) ▪ Rate of other non-pain complications (by age group) **Direct effects of vaccination** ▪ Proportion of subjects with vaccine related local/general adverse event (by age group) ▪ Proportion of subjects with vaccine related outpatient visit (by age group) ▪ Proportion of subjects with vaccine related emergency room visit (by age group) ▪ Proportion of subjects with vaccine related hospitalisation (all ages) **QALYs** ▪ Baseline utility values (by age group) ▪ QALY loss per HZ case without PHN unvaccinated (by age group) ▪ QALY loss per HZ case without PHN vaccinated (by age group) ▪ QALY loss per HZ case with PHN unvaccinated (by age group) ▪ QALY loss per HZ case with PHN vaccinated (by age group) ▪ QALY loss per vaccine related local/general adverse event ▪ QALY loss per vaccine related hospitalisation (serious adverse event)

Economic results		▪ Weighted adverse event-related QALY loss per vaccine dose based on proportion with a local/general reaction and proportion with a serious adverse event.
	Type of summary ratio	ICER
	Overall payer perspective result	N/A
	Overall societal perspective result	For individuals vaccinated at age: ▪ ≥60 years, RZV ICER = USD 11,863/QALY gained versus no vaccination ▪ ≥60 years, RZV dominated ZVL ▪ ≥60 years, RZV ICER = USD 38,867/QALY gained versus no vaccination (health sector perspective)
Authors conclusions	Vaccination against HZ with RZV is cost-effective compared to no vaccination and cost-saving compared to ZVL in the US population aged ≥60 years.	

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; PHN – post-herpetic neuralgia; QALY – quality-adjusted life year; RZV – recombinant zoster vaccine; USD – United States dollar; ZONA – ZOster ecoNomic Analysis; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Curran et al. 2021 DOI: 10.1080/21645515.2021.2002085	
	Region, Country	Germany	
	Type of Economic Evaluation	CUA	
	Population	Adults aged ≥50 years	
	Funding	Industry (GlaxoSmithKline Biologicals SA)	
Model characteristics	**Model type**	Multi-cohort Markov model (five age groups for people aged ≥50 years [i.e. 50–59, 60–64, 65–69, 70–79, ≥80]) with 1 year cycles (ZONA) Health states: 1. Healthy 2. HZ 3. PHN (from HZ and recurrent HZ) 4. Non PHN complications (from HZ and recurrent HZ) 5. Recovered 6. Recurrent HZ 7. Death from HZ 8. Death from other causes	
	Model software	Excel	
	Perspective	Not specified but assumed societal given indirect costs included	
	Time horizon	Lifetime	
	Comparator	No vaccination	
	Discount rates	3.0% for costs and outcomes	
	Sensitivity analysis	Deterministic and probabilistic	
Intervention strategy	**Vaccine type**	RZV	
	Dosing schedule	2-dose	
	Age at vaccination	Various: 50yrs, 60yrs, 65yrs, 70yrs, ≥50 years, ≥60 years, ≥70 years	
	Coverage rate	1st dose: 40%; 2nd dose: 70%	
Model input parameters	**Efficacy/effectiveness**	RZV 2-dose 50-69yrs: 98.9%; ≥70yrs: 95.4%	
	Waning	RZV 2-dose 50-69yrs: 1.5% p.a.; ≥70yrs: 2.3% p.a.	
	Costs included	**Type of cost** **Direct costs** ▪ Direct medical costs - HZ without PHN - HZ with PHN ▪ Vaccination costs - vaccine - administration - adverse events **Indirect costs** ▪ Included but not detailed	**Measurement and valuation** **Direct costs** ▪ Direct medical costs - EUR cost per HZ case (by age group) - EUR cost per PHN case (by age group) ▪ Vaccination costs - EUR cost per vaccine dose - EUR cost per vaccine dose administration - EUR cost per vaccine-related adverse event (by age group) **Indirect costs** ▪ Not detailed - EUR cost per HZ case (by age group) - EUR cost per PHN case (by age group)
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ PHN ▪ Non-PHN complications ▪ Recurrent HZ	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ and recurrence (by age group) ▪ Probability of PHN in HZ cases (by age group) ▪ Case fatality rate for HZ cases (by age group) **Direct effects of vaccination**

		▪ Recurrent HZ with PHN ▪ Disease-related deaths **Direct effects of vaccination** ▪ Not reported	▪ Not reported **QALYs** ▪ Baseline utility values (by age group) ▪ Disutility HZ only (by age group) ▪ Disutility HZ and PHN (by age group)
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	N/A	
	Overall societal perspective result	For individuals vaccinated at age: ▪ 50 years, RZV ICER = €29,547/QALY gained versus no vaccination ▪ 60 years, RZV ICER = €25,536/QALY gained versus no vaccination ▪ 65 years, RZV ICER = €26,116/QALY gained versus no vaccination ▪ 70 years, RZV ICER = €34,663/QALY gained versus no vaccination ▪ ≥50 years, RZV ICER = €31,735/QALY gained versus no vaccination ▪ ≥60 years, RZV ICER = €32,956/QALY gained versus no vaccination ▪ ≥70 years, RZV ICER = €39,676/QALY gained versus no vaccination	
Authors conclusions	Due to the higher, sustained, RZV vaccine effectiveness, improved public health and cost-effectiveness results were observed compared to previous analyses.		

Key: CUA – cost-utility analysis; EUR – Euro; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; ZONA – ZOster ecoNomic Analysis

General study characteristics	**Author Name, Year of Publication, DOI**	deBoer et al. 2018 DOI: 10.1186/s12916-018-1213-5
	Region, Country	Netherlands
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥50 years
	Funding	None
Model characteristics	**Model type**	Multi-cohort Markov model (annual cycles) with Decision Tree Health states Markov model: 1. Alive/Dead Health states Decision Tree: 1. HZ/No HZ 2. Hospitalisation/No hospitalisation 3. Dead from HZ/Dead from other causes
	Model software	Excel
	Perspective	Societal
	Time horizon	15 years (age maximum 115 years)
	Comparator	No vaccination
	Discount rates	4.0% for costs and 1.5% for outcomes
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Vaccine**	ZVL and RZV
	Dosing schedule	ZVL Single dose and single dose + booster (after 10 years) RZV 2-dose (2 month interval)
	Age at vaccination	Various: 50yrs, 60yrs, 70yrs and 80yrs
	Coverage rate	1st dose: 50%; 2nd dose: 100%
Model input parameters	**Efficacy/effectiveness**	ZVL Modelled using one-minus exponential function: 1-exp(β_{1+} β_2*(risk ratio of efficacy by age)), with values for intercept β_1, slope β_2 and risk ratio of efficacy by age provided RZV 50-69yrs: 98.1%; ≥70yrs: 99.2%
	Waning	ZVL 8.07% p.a. RZV 50-69yrs: 0.9% p.a. for Years 1-4 and 4.1% p.a. thereafter; ≥70yrs: 4.1% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Health care costs - GP visit, medication, specialist visit - hospital admission - 1-day hospital admission ▪ Vaccination costs - vaccine - administration ▪ Patient costs - over-the-counter medication - travel for GP visit, medication, specialist care - travel for hospital - travel for vaccination
		Measurement and valuation **Direct costs** ▪ Direct medical costs - number of GP visits per HZ case (by age group) and EUR unit cost per GP visit - proportion of specialist visits given referral, number of specialist visits (by age group) and EUR unit cost per specialist visit - probability of medication prescription (antiviral drugs, opiates, topical treatment, antiepileptic drugs, tricyclic antidepressant) and EUR unit cost per medication - length of hospitalisation (days) (by age group) and EUR unit cost per hospitalisation day - EUR unit cost per 1-day hospital admission ▪ Vaccination costs - EUR cost per vaccine dose - EUR cost per vaccine dose administration

		Indirect costs ▪ Unrelated healthcare costs in gained life years per averted HZ death ▪ Productivity losses due to work absenteeism and work presenteeism - HZ episode - HZ death	▪ Patient costs - Probability of OTC medication (pain killers, topical) and EUR unit cost per OTC medication (by age group) - EUR unit cost for travel to GP - EUR unit cost for travel to pharmacist - EUR unit cost for travel for hospital (per hospital visit/hospitalisation) - EUR cost for travel for vaccination (per dose) **Indirect costs** ▪ Unrelated healthcare costs in gained life years - life expectancy at age of death - yearly age-specific healthcare costs ▪ Productivity loss for HZ episode - absenteeism given HZ (days) (by age group) - presenteeism given HZ (days) (by age group) - EUR unit cost per lost labour day ▪ Productivity loss for HZ-related death (friction cost approach) - number of working days lost to HZ death - EUR unit cost per lost labour day
	Effects included	**Type of Effects** **Direct effects** ▪ HZ (adjusted for misdiagnoses of HZ) - no pain - mild pain - moderate pain (PHN if persists for >3 months) - severe pain (PHN if persists >3 months) ▪ Hospitalisation ▪ 1-day hospitalisation ▪ Disease-related deaths (adjusted for misclassification of HZ as underlying cause of death)	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ and recurrence (by age group) ▪ Percentage of false positive diagnoses ▪ Probability of HZ pain by severity over time (by age group) ▪ Incidence of hospitalisation (by age group) ▪ Incidence of disease-related mortality ▪ Percentage of misclassification of HZ as underlying cause of death ▪ Life years lost due to HZ-related premature mortality **QALYs** ▪ Baseline utilities and utilities of the different pain severity of HZ over time ▪ QALY loss per HZ episode by pain level (no pain, mild pain, moderate pain, severe pain) (by age group) ▪ QALY loss per HZ death (age specific) ▪ QALY loss per Grade 3 adverse event per dose per vaccine (not included in base-case scenario)
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	N/A	
	Overall societal perspective result	In the base-case scenario, for individuals vaccinated at age: ▪ 50 years, all three vaccination strategies dominated no vaccination ▪ 60 years, all three vaccination strategies dominated no vaccination ▪ 70 years, all three vaccination strategies dominated no vaccination ▪ 80 years, all three vaccination strategies dominated no vaccination	
Authors conclusions	A strategy with two doses of RZV was superior in reducing the burden of HZ as compared to a single dose or single dose + booster of ZVL. Both vaccines could potentially be cost effective to a conventional Dutch willingness-to-pay threshold for preventive interventions. However, whether RZV or ZVL would be the most cost effective alternative depends largely on the vaccine cost.		

Key: CUA – cost-utility analysis; EUR – Euro; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; OTC – over-the-counter; QALY – quality-adjusted life year; RZV – recombinant zoster vaccine; ZVL – herpes zoster live vaccine.

General study characteristics	**Author Name, Year of Publication, DOI**	Drolet et al. 2019 DOI: 10.1503/cmaj.190274
	Region, Country	Canada
	Type of Economic Evaluation	CUA
	Population	Adults aged ≥50 years
	Funding	Public Health Agency of Canada, the Ministère de la Santé et des Services Sociaux du Québec, the Canadian Institutes of Health Research (Foundation scheme grant FDN143283) and the Fonds de recherche du Québec – Santé (support to Marc Brisson).
Model characteristics	**Model type**	Decision analytic static cohort model Health states: 1. No HZ 2. HZ 3. PHN 4. Death
	Model software	Not reported
	Perspective	Health care system
	Time horizon	Lifetime
	Comparator	No vaccination and alternative vaccine
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic and probabilistic (LHS)
Intervention strategy	**Vaccine**	ZVL and RZV
	Dosing schedule	ZVL: 1-dose; RZV: 2-dose
	Age at vaccination	Various: 50yrs, 60yrs, 65yrs, 70yrs, 75yrs, 80yrs, 85yrs
	Coverage rate	Not provided.
Model input parameters	**Efficacy/effectiveness**	Estimated by fitting the age-specific annual incidence of herpes zoster predicted by the model with that observed in the vaccination arm of randomized clinical trials. Data not specified - calibration results of the predicted vaccine efficacy to vaccine efficacy from randomised clinical trials are provided in graphs in the supplementary file.
	Waning	Waning functions detailed in supplementary file but data not provided.
	Costs included	**Type of cost** **Direct costs** ▪ Health care costs - hospitalisation - consultation ▪ Vaccination costs - vaccines **Indirect costs** ▪ N/A
		Measurement and valuation **Direct costs** ▪ Health care costs - percentage of HZ cases hospitalised (by age group) - length of hospital stay in days (by age group) - CAD cost per HZ-related hospitalisation (per day) - number of consultations per HZ case (by age group) - CAD cost per HZ-related consultation - CAD cost for treatment of HZ (per episode) - CAD cost for treatment of PHN (per episode) ▪ Vaccination costs - CAD cost per course **Indirect costs** ▪ N/A
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ Ophthalmic HZ ▪ PHN
		Measurement and valuation **Direct effects** ▪ Incidence of HZ (by age group) ▪ Proportion of ophthalmic HZ ▪ PHN as a percentage of HZ cases (by age group)

		▪ Hospitalisation ▪ Death	▪ Hospitalisations as a percentage of HZ cases (by age group) ▪ Consultations per HZ case (by age group) ▪ Length of hospital stay (days) (by age group) ▪ Case-fatality rate (by age group) **QALYs** ▪ QALYs lost HZ (by age group) ▪ QALYs lost PHN (by age group)
Economic results	**Type of summary ratio**	ICER	
	Overall health care system perspective result	For individuals vaccinated at age: ▪ ≥50 years: median RZV ICERs varied between cost-saving and CAD 25,881/QALY gained versus no vaccination ▪ ≥50 years: median ZVL ICERs varied between cost-saving and CAD 130,587/QALY gained versus no vaccination ▪ 65 to 75 years old: median ZVL ICERs <CAD 45,000/QALY gained versus no vaccination	
	Overall societal perspective result	N/A	
Authors conclusions	The model predicted that the RZV vaccine is likely cost effective in Canada for adults aged ≥60 years, and is likely more cost effective than ZVL.		

Key: CAD – Canadian dollar; CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Flem et al. 2022 DOI: 10.1080/14737167.2021.1973893
	Region, Country	Norway
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥60 years
	Funding	Merck and Co., Inc.
Model characteristics	**Model type**	Multi-cohort decision analytic model Health states: 1. No HZ 2. HZ 3. PHN 4. Death
	Model software	Excel
	Perspective	1. Health care system 2. Societal
	Time horizon	40 years
	Comparator	No vaccination
	Discount rates	4.0% for costs and outcomes
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Vaccine**	ZVL
	Dosing schedule	1-dose
	Age at vaccination	Various: 60yrs (without and with catch-up in 60-70yr olds in the first year of the programme only) 65yrs (without and with catch-up in 65-70yr olds in the first year of the programme only) 70yrs (without and with catch-up in 70-80yr olds in the first year of the programme only)
	Coverage rate	Main cohort (non-catch-up): 30% in Yr1, 40% in Yr2, 50% in Yrs3+ Catch-up: 30%
Model input parameters	**Efficacy/effectiveness**	Data provided below have been read from a graph. <u>ZVL against HZ</u> 60-69yr olds: 70% at vaccination, 40% at 5yrs post-vaccination, 28% at 10yrs post-vaccination, 15% at 15yrs post-vaccination and 4% at 20yrs post-vaccination 70-79yr olds: 65% at vaccination, 33% at 5yrs post-vaccination, 12% at 10yrs post-vaccination, 0% at 15yrs post-vaccination ≥80yr olds: 65% at vaccination, 27% at 5yrs post-vaccination, 8% at 10yrs post-vaccination, 0% at 15yrs post-vaccination <u>ZVL against PHN</u> 60-69yr olds: 85% at vaccination, 60% at 5yrs post-vaccination, 45% at 10yrs post-vaccination, 28% at 15yrs post-vaccination, 13% at 20yrs post-vaccination and 0% at 25yrs post-vaccination 70-79yr olds: 85% at vaccination, 55% at 5yrs post-vaccination, 36% at 10yrs post-vaccination, 18% at 15yrs post-vaccination and 0% at 20yrs post-vaccination ≥80yr olds: 77% at vaccination, 56% at 5yrs post-vaccination, 39% at 10yrs post-vaccination, 22% at 15yrs post-vaccination, 4% at 20yrs post-vaccination and 0% at 25yrs post-vaccination
	Waning	Data not specifically provided but could be estimated from graphs of vaccine effectiveness over time
	Costs included	**<u>Type of cost</u>** **Direct costs** ▪ Health care treatment costs - primary care - medication - hospitalisation ▪ Vaccination costs - vaccine - vaccine administration - vaccine-related adverse events
		<u>Measurement and valuation</u> **Direct costs** ▪ Health care treatment costs - NOK cost for primary care (per case) - NOK cost for medication (per case) - NOK cost for hospitalisation (per case) ▪ Vaccination costs - NOK cost for vaccine (per dose) - NOK cost for vaccine administration (per dose) - NOK cost for treatment for a mild to moderate adverse event

	Effects included	○ mild to moderate reaction ○ severe reaction **Indirect costs** ▪ Productivity loss - absenteeism form work associated with HZ **<u>Type of Effects</u>** **Direct effects** ▪ HZ - no pain - mild pain - moderate pain - severe pain ▪ PHN ▪ Hospitalisation ▪ Death **Direct effects of vaccination** ▪ Vaccine-related adverse event - mild to moderate reaction (Grade 1-2) ○ injection-site reaction ○ systemic reaction ○ allergic reaction - severe reaction (Grade 3 and above) ○ injection-site reaction ○ systemic reaction ○ allergic reaction	- NOK cost for treatment for a severe adverse event **Indirect costs** ▪ Productivity loss - percentage employed (by sex and age group) - average hourly wage - absenteeism hours per case of HZ **<u>Measurement and valuation</u>** **Direct effects** ▪ Incidence of HZ (by sex and age group) ▪ Proportion of HZ cases with no pain (by age group) ▪ Proportion of HZ cases with mild pain (by age group) ▪ Proportion of HZ cases with moderate pain (by age group) ▪ Proportion of HZ cases with severe pain (by age group) ▪ Probability of PHN cases in HZ cases (by age group) ▪ Proportion of PHN cases with mild pain (by age group) ▪ Proportion of PHN cases with moderate pain (by age group) ▪ Proportion of PHN cases with severe pain (by age group) ▪ Probability of hospitalisation for a case of HZ (by age group) ▪ Case fatality rate **Direct effects of vaccination** ▪ Vaccine-related adverse event - Mild to moderate reaction ○ probability of injection-site reaction ○ probability of systemic reaction ○ probability of allergic reaction - severe reaction ○ probability of injection-site reaction ○ probability of systemic reaction ○ probability of allergic reaction **QALYs** ▪ Baseline health utility (by sex and age group) ▪ Utility and decrement for HZ (by pain severity) ▪ Utility and decrement for PHN (by pain severity) ▪ QALY loss for HZ (by sex and age group) ▪ QALY loss for PHN with no vaccine protection (by age group) ▪ QALY loss for PHN with vaccine protection (by age group) ▪ QALY loss for mild to moderate vaccine-related adverse events ▪ QALY loss for severe injection-site reaction to vaccine ▪ QALY loss for severe systemic reaction to vaccine ▪ QALY loss for severe allergic reaction to vaccine
Economic results	**Type of summary ratio** **Overall health care system perspective result**	ICER For individuals vaccinated at age: ▪ 60yrs without catch-up, ZVL ICER = NOK 274,701/QALY gained versus no vaccination ▪ 60yrs with catch-up, ZVL ICER = NOK 259,818/QALY gained versus no vaccination ▪ 65yrs without catch-up, ZVL ICER = NOK 253,105/QALY gained versus no vaccination ▪ 65yrs with catch-up, ZVL ICER = NOK 248,637/QALY gained versus no vaccination ▪ 70yrs without catch-up, ZVL ICER = NOK 317,281/QALY gained versus no vaccination ▪ 70yrs with catch-up, ZVL ICER = NOK 316,207/QALY gained versus no vaccination	

Authors conclusions	**Overall societal perspective result**	For individuals vaccinated at age: ▪ 60yrs without catch-up, ZVL ICER = NOK 259,559/QALY gained versus no vaccination ▪ 60yrs with catch-up, ZVL ICER = NOK 247,076/QALY gained versus no vaccination ▪ 65yrs without catch-up, ZVL ICER = NOK 249,898/QALY gained versus no vaccination ▪ 65yrs with catch-up, ZVL ICER = NOK 245,459/QALY gained versus no vaccination ▪ 70yrs without catch-up, ZVL ICER = NOK 314,066/QALY gained versus no vaccination ▪ 70yrs with catch-up, ZVL ICER = NOK 312,962/QALY gained versus no vaccination
	Vaccinating adults at 65 years of age with catch-up up to 70 years in the first year of the program was the most cost-effective strategy with the incremental cost per QALY gained at NOK 245,459 from the societal perspective and NOK 248,637 from the health care system perspective.	

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; NOK – Norwegian Krone; QALY – quality-adjusted life-year; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Hoshi et al. 2019 DOI: 10.1016/j.vaccine.2019.05.006.
	Region, Country	Japan
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged 65-84 years
	Funding	Supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan (H29-SHINKOGYOSEI-SHITEI-003).
Model characteristics	**Model type**	Decision tree (choice of vaccine strategy) and static Markov model (one year cycle) Health states: 1. Healthy 2. HZ 3. PHN 4. Recovery from HZ/PHN 5. Recurrent HZ 6. Dead
	Model software	TreeAge
	Perspective	Payer (including government, municipalities, vaccines, patients and third-party payers)
	Time horizon	Until cohort reached 100yrs old
	Comparator	Curative care scenario and next best alternative
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way) and probabilistic
Intervention strategy	**Vaccine**	RZV and VVL
	Dosing schedule	RZV: 1-dose and 2-dose (2-6 month interval between doses) VVL: 1-dose
	Age at vaccination	Various: 65-84yrs, 70-84yrs, 75-84yrs, 80-84yrs
	Coverage rate	Frist dose: 40.8%; second dose: 80%
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose 65-69yrs: 90%; ≥70yrs: 69.0% RZV 2-dose 65-69yrs: 100%; ≥70yrs: 97.0% VVL (Year 1) 65-69yrs: 70.6%; 70-79yrs: 64.5%; ≥80yrs: 63.7%
	Waning	1-dose RZV 65-69yrs: 9.1% p.a. (11yrs); ≥70yrs: 25% p.a. (4yrs) 2-dose RZV 65-69yrs: 5.15% p.a. (19.4yrs); ≥70yrs: 5.32% p.a. (18.8yrs) VVL 65-69yrs: waned to 0% at Yr9; 70-79yrs: waned to 0% at Yr8; ≥80yrs: waned to 0% at Yr7
	Costs included	**Type of cost** **Direct costs** ▪ Health care treatment costs - treatment ▪ Vaccination costs - vaccine - doctor's fee - technical fee **Measurement and valuation** **Direct costs** ▪ Health care treatment costs - JPY cost for treatment of HZ case (by age group) - JPY cost for treatment of PHN case (by age group) ▪ Vaccination costs - JPY and USD cost for vaccination (per dose)
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ PHN ▪ Recurrent HZ (one-time) **Measurement and valuation** **Direct effects** ▪ Age- and sex-specific incidence of HZ ▪ Age- and sex-specific proportion of recurrence of HZ ▪ Age- and sex-specific probability of PHN cases among HZ cases

		▪ Death	▪ Death rates
		Direct effects of vaccination ▪ Vaccine-related Grade 3 solicited systemic adverse events (myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms) included in sensitivity analysis only	**Direct effects of vaccination** ▪ Percentage of HZ cases with vaccine-related Grade 3 solicited systemic events (by vaccine) **QALYs** ▪ Utility weights HZ (by age group) ▪ Utility weights PHN (by age group)
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	For individuals vaccinated at age: ▪ 65-84yrs, RZV ICER = JPY 6,278,557 (USD 57,078)/QALY gained versus curative care scenario ▪ 70-84yrs, RZV ICER = JPY 5,629,590/QALY gained versus curative care scenario ▪ 75-84yrs, RZV ICER = JPY 5,561,451/QALY gained versus curative care scenario ▪ 80-84yrs, RZV ICER = JPY 5,262,227/QALY gained versus curative care scenario ▪ 65-84yrs, VVL ICER = JPY 3,434,267/QALY gained versus curative care scenario ▪ 70-84yrs, VVL ICER = JPY 2,961,041/QALY gained versus curative care scenario ▪ 75-84yrs, VVL ICER = JPY 2,902,059/QALY gained versus curative care scenario ▪ 80-84yrs, VVL ICER = JPY 2,633,587/QALY gained versus curative care scenario For individuals vaccinated at age: ▪ 65-84yrs, RZV ICER = JPY 8,888,295/QALY gained versus next best alternative (VVL 65-84yrs) ▪ 65-84yrs, VVL ICER = JPY 4,540,425/QALY gained versus next best alternative (VVL 70-84yrs)	
	Overall societal perspective result	N/A	
Authors conclusions	Vaccinating individuals aged 65-84yrs, 70-84yrs, 75-84yrs, 80-84yrs with VVL or RZV to prevent HZ-associated disease in Japan can be cost-effective from payer's perspective, with vaccination costs at ¥8,000 (US$73) per shot for VVL, ¥30,000 (US$280) for 2-dose RZV. The results of PSA suggest that only the 65-84yrs VVL-strategy and 65-84yrs RZV strategy should be considered when introducing HZ immunisation programme. The optimal strategy varies depending on the WTP threshold.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; JPY – Japanese yen; N/A – not applicable; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; USD – United States dollar; VVL – live varicella vaccine; WTP – willingness-to-pay

General study characteristics	**Author Name, Year of Publication, DOI**	McGirr et al. 2019 DOI: 10.1007/s40258-019-00491-6
	Region, Country	Canada
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥60yrs (secondary analysis conducted in persons aged ≥50yrs)
	Funding	GlaxoSmithKline Biologicals SA
Model characteristics	**Model type**	Multi-cohort Markov model (ZONA) (cycle length one year) Health states: 1. Healthy 2. HZ 3. PHN (from HZ and recurrent HZ) 4. Non PHN complications (from HZ and recurrent HZ) 5. Recovered 6. Recurrent HZ 7. Death from HZ 8. Death from other causes
	Model software	Excel
	Perspective	Healthcare payer
	Time horizon	Lifetime
	Comparator	No vaccination and alternative vaccine
	Discount rates	1.5% for costs and outcomes
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Vaccine**	ZVL and RZV
	Dosing schedule	ZVL: 1-dose; RZV: 2-dose
	Age at vaccination	≥60yrs (and ≥50yrs in supplementary analysis)
	Coverage rate	ZVL: 80% RZV: first dose 80%; second dose 75%
Model input parameters	**Efficacy/effectiveness**	ZVL HZ: 50-59yrs: 69.8%; 60-64yrs: 63.89%; 65-69yrs: 63.89%; 70-79yrs: 40.85%; ≥80yrs: 18.25% PHN: 50-59yrs: 69.8%; 60-64yrs: 65.69%; 65-69yrs: 65.69%; 70-79yrs: 73.38%; ≥80yrs: 39.51% RZV 1-dose (HZ and PHN) 50-59yrs: 90.0%; 60-64yrs: 90.0%; 65-69yrs: 90.0%; 70-79yrs: 69.5%; ≥80yrs: 69.5% RZV 2-dose (HZ and PHN) 50-59yrs: 98.4%; 60-64yrs: 98.4%; 65-69yrs: 98.4%; 70-79yrs: 97.84%; ≥80yrs: 97.84%
	Waning	ZVL All age cohorts: 5.4% p.a. for the first four years and 5.1% p.a. thereafter 2-dose RZV 50-59yrs, 60-64yrs and 65-69yrs: 1.0% p.a. for first four years and 2.3% p.a. thereafter 70-79yrs and ≥80yrs: 3.6% p.a. constant
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ - PHN ▪ Vaccination costs - vaccine - administration - vaccine-related adverse events requiring a medically attended visit (GP, ER and or hospitalisation) **Measurement and valuation** **Direct costs** ▪ Medical costs - CAD cost per HZ case (by age group) - CAD cost per PHN case (by age group) ▪ Vaccination costs - CAD cost per vaccine dose - CAD cost for administration of first dose - CAD cost for administration of second dose - CAD cost due to adverse events per vaccinated individual, RZV (by age group) - CAD cost due to adverse events per vaccinated individual, ZVL

			(by age group)
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ HZ with PHN ▪ Non PHN complications - neurological - ocular - cutaneous - non-pain complications ▪ Recurrent HZ ▪ Death **Direct effects of vaccination** ▪ Vaccine-related adverse event - local/general reaction - reaction leading to GP visit - reaction leading to ER visit - serious reaction leading to hospitalisation	**Measurement and valuation** **Direct effects** ▪ Annual probability of initial and recurrent HZ (by age group) ▪ Percentage of PHN three months after initial or recurrent HZ (by age group) ▪ Complication rates - rate of ocular complications (by age group) - rate of neurological complications (by age group) - rate of cutaneous complications (by age group) - rate of other non-pain complications (by age group) ▪ Case-fatality rate for HZ cases (by age group) **Direct effects of vaccination** ▪ Vaccine-related adverse event - probability of local/general reaction by vaccine (by age group) - probability of reaction leading to GP visit by vaccine (by age group) - probability of reaction leading to ER visit by vaccine (by age group) - probability of serious reaction leading to hospitalisation by vaccine (by age group) - length of stay (hospitalisation) for a vaccine-related serious adverse event **QALYs** ▪ Baseline utility by age group ▪ QALY loss per HZ-only case ▪ QALY loss per PHN-only case ▪ QALY loss per local/general vaccine-related adverse event ▪ QALY loss per serious (hospitalisation) vaccine-related adverse event
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	For individuals vaccinated at age: ▪ ≥60yrs, RZV ICER = CAD 28,360/QALY gained versus no vaccination ▪ ≥60yrs, RZV ICER = CAD 2,396/QALY gained versus ZVL	
	Overall societal perspective result	N/A	
Authors conclusions	The cost-utility analysis suggested that RZV would be cost effective in the Canadian population compared with no vaccination and vaccination with ZVL, at a willingness-to-pay threshold of CAD 50,000. Results for the Canadian population aged ≥50 years were similar.		

Key: CAD – Canadian dollar; CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; ZONA – ZOster ecoNomic Analysis; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Melegaro et al. 2018 DOI: 10.1186/s12916-018-1094-7	
	Region, Country	Italy	
	Type of Economic Evaluation	CUA	
	Population	Adults aged ≥65yrs	
	Funding	European Research Council (ERC) under the European Union's Seventh Framework Programme (FP7/2007–2013) and ERC Grant agreement number 283955 (DECIDE)	
Model characteristics	**Model type**	Stochastic individual-based epidemiological model and decision tree for cost-effectiveness model (impact of varicella vaccination also modelled but DE relates to HZ vaccination only) Health states: 1. Susceptible to HZ 2. Recovered from HZ	
	Model software	C and R	
	Perspective	Taxpayer	
	Time horizon	25yrs (short), 50yrs (medium) and 85yrs (long-term)	
	Comparator	No vaccination	
	Discount rates	3% for costs and outcomes	
	Sensitivity analysis	Probabilistic	
Intervention strategy	**Vaccine**	ZVL	
	Dosing schedule	1-dose	
	Age at vaccination	≥65yrs either alone or in combination with an initial catch-up campaign (66-75yrs)	
	Coverage rate	60%	
Model input parameters	**Efficacy/effectiveness**	Efficacy: 50%	
	Waning	Not incorporated	
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - GP visits - treatment - hospitalisation ▪ Vaccination cost - vaccine - vaccine administration **Indirect costs** ▪ N/A	**Measurement and valuation** **Direct costs** ▪ Medical costs - outpatient cost per case of HZ (incl. visit, treatment and diagnostics) - outpatient cost per case of PHN (incl. visit, treatment and diagnostics) - hospitalisation rate for HZ (<49yrs and ≥50yrs) - hospitalisation rate for PHN (<49yrs and ≥50yrs) - hospitalisation cost per case of HZ (by age - <49yrs and ≥50yrs) - hospitalisation cost per case of PHN (by age - <49yrs and ≥50yrs) ▪ Vaccination cost - cost per dose of vaccine - admin cost per dose of vaccine **Indirect costs** ▪ N/A
	Effects included	**Type of Effects** **Direct effects** ▪ Averted cases of HZ without PHN ▪ Averted cases of HZ with PHN ▪ Averted deaths	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ (by age group) ▪ Proportion of cases developing PHN (by age) ▪ HZ-PHN case fatality rate of hospitalised cases. **QALYs** ▪ QALY loss HZ 20yrs

		▪ QALY loss HZ 40yrs ▪ QALY loss HZ 60yrs ▪ QALY loss HZ 80yrs ▪ QALY loss for death
Economic results	**Type of summary ratio**	ICER
	Overall taxpayer perspective result	HZ vaccination only and assuming temporary complete immunity due to EB: ZVL ICER = €17,333/QALY gained versus no vaccination for the 25yr time horizon ZVL ICER = €9,520/QALY gained versus no vaccination for the 50yr time horizon ZVL ICER = €8,418/QALY gained versus no vaccination for the 75yr time horizon HZ vaccination + catch-up and assuming temporary complete immunity due to EB: ZVL ICER = €13,480/QALY gained versus no vaccination for the 25yr time horizon ZVL ICER = €9,252/QALY gained versus no vaccination for the 50yr time horizon ZVL ICER = €8,452/QALY gained versus no vaccination for the 75yr time horizon HZ vaccination only and assuming progressive partial immunity due to EB: ZVL ICER = €12,263/QALY gained versus no vaccination for the 25yr time horizon ZVL ICER = €6,029/QALY gained versus no vaccination for the 50yr time horizon ZVL ICER = €4,989/QALY gained versus no vaccination for the 75yr time horizon HZ vaccination + catch-up and assuming progressive partial immunity due to EB: ZVL ICER = €10,340/QALY gained versus no vaccination for the 25yr time horizon ZVL ICER = €6,253/QALY gained versus no vaccination for the 50yr time horizon ZVL ICER = €5,336/QALY gained versus no vaccination for the 75yr time horizon
	Overall societal perspective result	N/A
Authors conclusions	The study has shown that the newly introduced combined varicella and HZ vaccination strategy in Italy is expected to be effective and cost effective in reducing the burden of disease and the loss of quality of life. We also found that an additional catch-up campaign for HZ vaccination targeting people aged 66-75yrs would further increase the benefits of the combined programme, leading to an additional reduction of 3,542 cases of HZ and 6 HZ-related deaths per year.	

Key: CUA – cost-utility analysis; EB – exogenous boosting; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Pieters et al. 2022 DOI: 10.1007/s40273-021-01099-2
	Region, Country	Belgium
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥50yrs to 85yrs
	Funding	This work was supported in part by Research Foundation-Flanders (JB), the Methusalem financing program of the Flemish government (ZP).
Model characteristics	**Model type**	Multi-cohort Markov decision tree with annual cycles Health states: 1. Healthy 2. HZ 3. HZ with hospitalisation 4. Death due to HZ
	Model software	R
	Perspective	Healthcare payer
	Time horizon	Lifetime of cohort until 103yrs old
	Comparator	No vaccination and alternative vaccine
	Discount rates	3.0% for costs and 1.5% for outcomes
	Sensitivity analysis	Probabilistic
Intervention strategy	**Vaccine**	ZVL and RZV
	Dosing schedule	ZVL: 1-dose and 1-dose with 10yr booster ; RZV: 2-dose (within two months)
	Age at vaccination	50yrs, 60yrs, 70yrs, 80yrs and 85yrs
	Coverage rate	First dose all vaccines: 46.2% Second dose/booster: 100%
Model input parameters	**Efficacy/effectiveness**	Note: Values used not clear as data not provided. ZVL During the RCT, it was observed that the vaccine efficacy depended on the age at vaccination. Therefore, the intercept of the 1-minus-exponential function was adjusted, including age-specific relative risk ratios, to include the effect of initial protection of ZVL depending on age. Efficacy at vaccination (read from graph) 50yr olds: 66%; 60yr olds: 66%; 70yr olds: 50%; 80yr olds: 25%; 85yr olds: 15% RZV (from RCT data) ≥50yrs: 98.4% ≥70yrs: 97.6%
	Waning	ZVL In order to estimate the duration of protection, the following were fitted: (1) functions with an elbow shape, (2) linear functions, and (3) functions with a knee shape. The best fit, corresponding to the lowest AIC, is given by the one-minus-exponential function. It was assumed that the waning rate was the same for all ages and that for the ZVL booster was the same as for ZVL. RZV Several functions were fitted to obtain the best fit for the vaccine efficacy of RZV (in ≥50yr olds and ≥70yr olds) over time. However, due to the limited follow-up (average of 3.2 and 3.7 years, respectively), all functions provided a similar fit in both trials. Therefore, the functions giving the longest and shortest duration of protection were used. In both age groups, a logarithmic function provided the longest duration of protection and the 1-minus-exponential the shortest duration of protection.
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ (by pain severity) - PHN (by pain severity) ▪ Vaccination costs - vaccine - administration **Measurement and valuation** **Direct costs** ▪ Medical costs - EUR cost per ambulatory HZ patient by pain severity (no pain, mild pain, moderate pain, severe pain) - EUR cost per ambulatory PHN patient by pain severity (moderate pain, severe pain) - EUR cost per hospitalised HZ patient by pain severity (no pain, mild pain, moderate pain, severe pain) - EUR cost per hospitalised PHN patient by pain severity

			(moderate pain, severe pain) ▪ Vaccination costs - EUR cost per vaccine dose - EUR cost for administration
	Effects included	**Type of Effects** **Direct effects** ▪ HZ by pain severity - no pain - mild pain - moderate pain - severe pain ▪ PHN by pain severity - no pain - mild pain - moderate pain - severe pain ▪ Hospitalisation ▪ Death **Direct effects of vaccination** ▪ N/A	**Measurement and valuation** **Direct effects** ▪ Proportion of PHN per HZ case (by age group) ▪ HZ hospitalisation rate (by age) ▪ Proportion of HZ and PHN patients (<70yrs and ≥70yrs) by pain severity - no pain - mild pain - moderate pain - severe pain ▪ HZ mortality rate (by age group) ▪ Duration of HZ (days) by age (<70yrs and ≥70yrs) ▪ Duration of PHN (days) by age (<70yrs and ≥70yrs) **Direct effects of vaccination** ▪ N/A **QALYs** ▪ Utility no pain ▪ QALY weight mild pain (%) ▪ Utility mild pain ▪ QALY weight moderate pain (%) ▪ Utility moderate pain ▪ QALY weight severe pain (%)
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	▪ At a price of €140.26 per dose and assuming logarithmic waning, vaccinating 50yr olds with RZV becomes cost effective compared with no vaccination program at a WTP threshold of €90,000/QALY gained or more. ▪ The incremental cost per QALY gained of RZV compared with no vaccination increases with increasingly older cohorts. ▪ If assuming 1-minus-exponential waning for RZV, vaccination with RZV will only become cost effective in 80 and 85yr olds at a WTP threshold of respectively €155,000 and €150,000. ▪ Vaccination with RZV, assuming logarithmic waning and a price of €140.26 per dose is less expensive per QALY gained compared with vaccination with ZVL (with and without booster) for all of the vaccinated cohorts. ▪ ZVL with and without booster will never be the optimal strategy at a price of €137.40 per dose.	
	Overall societal perspective result	N/A	
Authors conclusions	RZV is cost-effective in the 50-year-old age cohort at the unofficial Belgian threshold of €40,000/QALY gained, if its price drops to €55.40 per dose. This result is, however, very sensitive to the assumed duration of protection of the vaccine, and the assumed severity and QALY loss associated with HZ and PHN. ZVL or ZVL with booster was never found cost effective compared with RZV for any of the threshold values considered. Only if the price per dose of ZVL or ZVL with booster would drop to €8.44 and €4.68, would it become cost effective compared with RZV at a WTP threshold of €40,000/QALY gained, for 60yr olds only.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; N/A – not applicable; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; WTP – willingness-to-pay; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Prosser et al. 2019	DOI: 10.7326/M18-2347
	Region, Country	USA	

Model characteristics	**Type of Economic Evaluation**	CUA
	Population	Immunocompetent adults aged ≥50yrs
	Funding	Centers for Disease Control and Prevention (CDC)
	Model type	Simulation (state-transition) model (Decision Tree) for hypothetical cohort stratified by age (annual cycles) Health states: 1. Disease free 2. Uncomplicated HZ 3. PHN 4. Other complications 5. Post HZ 6. Recurrent HZ 7. Dead from HZ 8. Dead from other cause
	Model software	TreeAge
	Perspective	1. Healthcare sector 2. Societal
	Time horizon	Lifetime
	Comparator	No vaccination and alternative vaccine
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way and multi-way) and probabilistic
Intervention strategy	**Vaccine**	ZVL and RZV
	Dosing schedule	ZVL: 1-dose; RZV: 2-dose
	Age at vaccination	Various: 50-59yrs, 60-69yrs, 70-79yrs, 80-89yrs, 90-99yrs
	Coverage rate	ZVL: not reported ; RZV 1-dose and 2-dose: 100%
Model input parameters	**Efficacy/effectiveness**	ZVL 50yr olds: 78.1%; 60yr olds: 77.9; 70yr olds: 65.9%; 80yr olds: 38.5%; 90yr olds: 9.5% RZV 1-dose 50-69yrs: 90%; ≥70yrs: 69% RZV 2-dose 50-69yrs: 100%; ≥70yrs: 97.0%
	Waning	ZVL (waning duration) 50yr olds: 12yrs; 60yr olds: 10yrs; 70yr olds: 7yrs; 80yr olds: 4yrs; 90yr olds: 1yr RZV 1-dose (waning duration) 50-69yrs: 11yrs ≥70yrs: 4yrs RZV 2-dose (waning duration) 50-69yrs: 19.4yrs ≥70yrs: 18.8yrs
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ uncomplicated - PHN - HZ complications o ocular o neurological o cosmetic ▪ Vaccination costs - vaccine - administration - adverse events
		Measurement and valuation **Direct costs** ▪ Medical costs - USD cost per uncomplicated HZ case (by age group) - USD cost per PHN case (by age group) - USD cost per case with ocular complications - USD cost per case with neurological complications - USD cost per case with skin complications ▪ Vaccination costs - USD cost per vaccine dose (by vaccine) - USD cost for administration - USD cost per non-Grade 3 injection site reaction

		○ injection site reactions ○ systemic reactions **Indirect costs** ▪ Productivity loss associated with disease -HZ -PHN ▪ Productivity loss associated with vaccination - patient time for vaccination-specific visit to physician's office - patient time for vaccination-specific visit to pharmacy - patient time for ED visit for vaccine-related adverse event	- USD cost per Grade 3 injection site reaction - proportion of patients requiring provider's visit for systemic reaction - USD cost per non-Grade 3 system reaction - USD cost per Grade 3 systemic reaction - proportion of patients requiring ED visit for vaccine-related adverse event - USD cost of ED visit for vaccine-related adverse event **Indirect costs** ▪ Productivity loss associated with disease - USD loss per case of HZ - USD loss per case of PHN (by age group) ▪ Productivity loss associated with vaccination - proportion of patients requiring health care provider's visit - proportion of patients receiving vaccine in pharmacy setting - patient time (hours) for vaccination-specific visit to physician's office - patient time (hours) for vaccination-specific visit to pharmacy - proportion of patients requiring ED visit for vaccine-related adverse event - patient time (hours) for ED visit for vaccine-related adverse event - mean hourly earnings
Effects included	**<u>Type of Effects</u>** **Direct effects** ▪ HZ ▪ HZ complications - ocular - neurologic - cosmetic ▪ Recurrent HZ ▪ PHN ▪ Death **Direct effects of vaccination** ▪ Adverse events - injection site reactions - systemic reactions - serious adverse events	**<u>Measurement and valuation</u>** **Direct effects** ▪ HZ incidence (by age) ▪ Conditional probability of PHN given HZ (by age group) ▪ Probability of ocular complications ▪ Probability of neurological complications ▪ Probability of cosmetic complications ▪ Probability of recurrent HZ ▪ HZ mortality rate (by age group) **Direct effects of vaccination** ▪ Adverse events - probability of Grade 1-2 injection site reactions (by vaccine) - probability of Grade 3 injection site reactions (by vaccine) - probability of Grade 1-2 systemic reactions (by vaccine) - probability of Grade 3 systemic reactions (by vaccine) - probability of co-occurrence of Grade 3 systemic and injection site reactions given AE (by vaccine) - probability of severe adverse event (by vaccine) **QALYs** ▪ Baseline health utility weights, age/sex adjusted ▪ QALY losses uncomplicated HZ (days per case) (by age group) ▪ QALY losses PHN (days per case) (by age group) ▪ QALY losses ocular complications (days per case) (by age group) ▪ Vaccine-related quality adjustments - non-grade 3 injection site reaction

		- Grade 3 injection site reaction - non-grade 3 systemic reaction - Grade 3 systemic reaction - serious adverse event
Economic results	**Type of summary ratio**	ICER
	Overall payer perspective result	For individuals vaccinated at age: ▪ 50-59yrs, RZV ICER = USD 60,814/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 60-69yrs, RZV ICER = USD 37,056/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 70-79yrs, RZV ICER = USD 20,333/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 80-89yrs, RZV ICER = USD 16,544/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 90-99yrs, RZV ICER = USD 32,373/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ For persons aged ≥60rs, ICER = USD 28,676/QALY gained.
	Overall societal perspective result	For individuals vaccinated at age: ▪ 50-59yrs, RZV ICER = USD 46,824/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 60-69yrs, RZV ICER = USD 25,683/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 70-79yrs, RZV ICER = USD 11,561/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 80-89yrs, RZV ICER = USD 9,739/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ 90-99yrs, RZV ICER = USD 27,310/QALY gained versus no vaccination, RZV dominant versus ZVL ▪ For persons aged ≥60rs, ICER = USD 19,015/QALY gained.
Authors conclusions	Vaccination with RZV yields cost-effectiveness ratios lower than those for many recommended adult vaccines, including ZVL. Results are robust over a wide range of plausible values.	

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; USD – United States dollar; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	Shiragami et al. 2019 DOI: 10.1007/s13555-019-0291-4
	Region, Country	Japan
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥50yrs partitioned into five age groups (50-59yrs, 60-64yrs, 65-69yrs, 70-79yrs and ≥80yrs)
	Funding	GlaxoSmithKline Biologicals SA
Model characteristics	**Model type**	Multi-cohort static Markov model (cycle length one year) (ZONA) Health states: 1. No HZ 2. HZ 3. PHN 4. HZ related complications (non PHN) 5. Recurrent HZ 6. HZ related death 7. Death due to natural causes
	Model software	Not reported
	Perspective	1. Payer 2. Societal (scenario analysis)
	Time horizon	Remaining lifetime of cohort
	Comparator	No vaccination
	Discount rates	2.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way) and probabilistic
Intervention strategy	**Vaccine**	RZV
	Dosing schedule	2-dose RZV
	Age at vaccination	≥65yrs base case (plus ≥50yrs, ≥60yrs, ≥70yrs)
	Coverage rate	First dose: 40%; second dose: 95%
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose 50-69yrs: 90.0%; ≥70yrs: 69.5% RZV 2-dose 50-69yrs: 98.4%; ≥70yrs: 97.84%
	Waning	RZV 1-dose Years 1-4: 5.4% p.a. Years 5+: 5.1% p.a. RZV 2-dose <70yrs: 1.0% p.a. in years 1-4; 2.3% p.a. year 5+ ≥70yrs: 3.6% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ uncomplicated - HZ with PHN - HZ with non PHN-related complications ▪ Vaccination costs - vaccine - administration - adverse events o local/general o outpatient o ER o hospitalisation
		Measurement and valuation **Direct costs** ▪ Medical costs - JPY cost per HZ case without complications - JPY cost per HZ case with PHN - JPY cost per HZ case with non PHN-related complications ▪ Vaccination costs - JPY cost per vaccine dose - JPY cost for administration per dose - JPY cost for local/general adverse event - JPY cost for outpatient visit for adverse event - JPY cost for ED visit for adverse event - JPY cost for hospitalisation for adverse event **Indirect costs**

		Indirect costs ▪ Productivity loss associated with disease for patients and caregivers - HZ without PHN - HZ with PHN	▪ Productivity loss - JPY cost per HZ case without PHN (by age group) - JPY cost per HZ case with PHN (by age group)
	Effects included	**Type of Effects** **Direct effects** ▪ Initial HZ ▪ Recurrent HZ ▪ Initial and recurrent HZ with PHN ▪ HZ-related complications other than PHN ▪ Death **Direct effects of vaccination** ▪ Adverse events - local/general - outpatient visit - ER visit - serious (hospitalisation)	**Measurement and valuation** **Direct effects** ▪ Incidence of initial and recurrent HZ (by age group) ▪ Percentage of initial and recurrent HZ cases with PHN (by age group) ▪ Probability of HZ-related complications other than PHN (by age group) ▪ HZ mortality rate (by age group) **Direct effects of vaccination** ▪ Adverse events - probability of local/general adverse event (by age group) - probability of outpatient visit for adverse event (by age group) - probability of ER visit for adverse event (by age group) - probability of hospitalisation for adverse event **QALYs** ▪ Baseline utility (by age group) ▪ QALY loss per HZ case without PHN (by age group) ▪ QALY loss per HZ case with PHN (by age group) ▪ QALY loss from vaccine-related local/general adverse event (implicitly assumed that persons requiring an outpatient ER visit for adverse events experienced the QALY loss related to a local/general reaction) ▪ QALY loss from vaccine-related adverse event requiring hospitalisation
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	For individuals vaccinated at age: ▪ ≥65yrs, RZV ICER = JPY 4,316,457/QALY gained versus no vaccination ▪ ≥50yrs, RZV ICER = JPY 4,518,465/QALY gained versus no vaccination ▪ ≥60yrs, RZV ICER = JPY 4,336,202/QALY gained versus no vaccination ▪ ≥70yrs, RZV ICER = JPY 4,374,192/QALY gained versus no vaccination	
	Overall societal perspective result	For individuals vaccinated at age: ▪ ≥65yrs, RZV ICER = JPY 4,036,020/QALY gained versus no vaccination ▪ ≥50yrs, RZV ICER = JPY 4,144,421/QALY gained versus no vaccination ▪ ≥60yrs, RZV ICER = JPY 4,034,556/QALY gained versus no vaccination ▪ ≥70yrs, RZV ICER = JPY 4,117,791/QALY gained versus no vaccination	
Authors conclusions	Vaccination against HZ with RZV would be cost effective compared with no vaccination for the Japanese population aged ≥65 years.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; JPY – Japanese yen; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; ZONA – ZOster ecoNomic Analysis

General study characteristics	**Author Name, Year of Publication, DOI**	Teng et al. 2022 DOI: 10.1007/s13555-022-00744-8 (Note: Update of Shiragami et al. [using longer term follow-up efficacy data and updated vaccine price])

Model characteristics	**Region, Country**	Japan
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥65yrs
	Funding	GlaxoSmithKline Biologicals SA
	Model type	Multi-cohort static Markov model (cycle length one year) (ZONA) Health states: 1. No HZ 2. HZ 3. PHN 4. HZ related complications (non PHN) 5. Recurrent HZ 6. HZ related death 7. Death due to natural causes
	Model software	Excel
	Perspective	1. Payer 2. Societal
	Time horizon	Remaining lifetime of cohort
	Comparator	No vaccination
	Discount rates	2.0% for costs and outcomes
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Vaccine**	RZV
	Dosing schedule	2-dose (two month interval between doses)
	Age at vaccination	65yrs base case (plus ≥50yrs, ≥65yrs, 50yrs, 60yrs, 70yrs, 80yrs)
	Coverage rate	First dose: 40%; second dose: 95%
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose efficacy against HZ and PHN 50-69yrs: 90.0%; ≥70yrs: 69.5% RZV 2-dose efficacy against HZ and PHN 50-69yrs: 98.9%; ≥70yrs: 95.4%
	Waning	RZV 1-dose Years 1-4: 5.4% p.a. Years 5+: 5.1% p.a. RZV 2-dose 50-69yrs: 1.5% p.a. ≥70yrs: 2.3% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ uncomplicated - HZ with PHN - HZ with non PHN-related complications ▪ Vaccination costs - vaccine - administration - adverse events o local/general o outpatient o ER o serious (hospitalisation) **Indirect costs**
		Measurement and valuation **Direct costs** ▪ Medical costs - JPY cost per HZ case without complications - JPY cost per HZ case with PHN - JPY cost per HZ case with non PHN-related complications ▪ Vaccination costs - JPY cost per vaccine dose - JPY cost for administration per dose - JPY cost for local/general adverse event - JPY cost for outpatient visit for adverse event - JPY cost for ED visit for adverse event - JPY cost for hospitalisation for adverse event - weighted JPY cost per adverse event per dose **Indirect costs**

		▪ Productivity loss associated with disease for patients and caregivers - HZ without PHN - HZ with PHN ▪ Productivity loss associated with time for vaccination	▪ Productivity loss associated with disease for patients and carers - JPY cost per HZ case without PHN (by age group) - JPY cost per HZ case with PHN (by age group) ▪ Productivity loss associated with time for vaccination - JPY cost per vaccinated individual (by age group)
	Effects included	**Type of Effects** **Direct effects** ▪ HZ uncomplicated ▪ HZ with PHN ▪ HZ with non PHN-related complications ▪ Death **Direct effects of vaccination** ▪ Adverse events - local/general - outpatient - ER - serious (hospitalisation)	**Measurement and valuation** **Direct effects** ▪ Incidence of initial and recurrent HZ (by age group) ▪ Percentage of initial and recurrent HZ cases with PHN (by age group) ▪ Probability of HZ-related complications other than PHN (by age group) ▪ HZ mortality rate (by age group) **Direct effects of vaccination** ▪ Adverse events - probability of local/general adverse event (by age group) - probability of outpatient visit for adverse event (by age group) - probability of ED visit for adverse event (by age group) - probability of serious (hospitalisation) for adverse event (by age group) **QALYs** (per Sharagmi et al.) ▪ Baseline utility (by age group) ▪ QALY loss per HZ case without PHN (by age group) ▪ QALY loss per HZ case with PHN (by age group) ▪ QALY loss from vaccine-related local/general adverse event (assumed persons requiring an outpatient/ER visit for adverse events experience the QALY loss related to a local/general reaction) ▪ QALY loss from vaccine-related adverse event requiring hospitalisation
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	For individuals vaccinated at age: ▪ 65yrs, RZV ICER = JPY 4,205,515/QALY gained versus no vaccination ▪ 50yrs, RZV ICER = JPY 4,698,221/QALY gained versus no vaccination ▪ 60yrs, RZV ICER = JPY 4,317,144/QALY gained versus no vaccination ▪ 70yrs, RZV ICER = JPY 4,290,994/QALY gained versus no vaccination ▪ 80yrs, RZV ICER = JPY 5,212,264/QALY gained versus no vaccination ▪ ≥50yrs, RZV ICER = JPY 4,547,684/QALY gained versus no vaccination ▪ ≥65yrs, RZV ICER = JPY 4,533,853/QALY gained versus no vaccination	
	Overall societal perspective result	For individuals vaccinated at age: ▪ 65yrs, RZV ICER = JPY 3,854,192/QALY gained versus no vaccination when productivity loss from HZ suffering only included ▪ 65yrs, RZV ICER = JPY 4,622,212/QALY gained versus no vaccination when productivity loss from HZ suffering and time required for vaccination included ▪ ≥65yrs, RZV ICER = JPY 4,244,476/QALY gained versus no vaccination when productivity loss from HZ suffering only included ▪ ≥65yrs, RZV ICER = JPY 4,614,515/QALY gained versus no vaccination when productivity loss from HZ suffering and time required for vaccination included	
Authors conclusions	Vaccination against HZ with RZV is cost effective compared with no vaccination in Japanese adults aged 65 years at the up-to-date vaccine price, given the high and sustained efficacy of RZV observed from long-term data.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; JPY – Japanese yen; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; ZONA – Zoster ecoNOmic Analysis

General study characteristics	**Author Name, Year of Publication, DOI**	Van Oorschot et al. 2019 DOI: 10.1080/21645515.2018.1509645
	Region, Country	Germany
	Type of Economic Evaluation	CUA
	Population	Immunocompetent adults aged ≥60yrs in the German statutory health insurance setting
	Funding	GlaxoSmithKline Biologicals SA
Model characteristics	**Model type**	Multi-cohort static Markov model (annual cycles) (ZONA) Health states: 1. No HZ 2. HZ 3. PHN (Note: Although model diagram includes non-PHN complications, no relevant data provided) 4. Recovered 5. Recurrent HZ 6. Death from HZ 7. Death from natural causes
	Model software	Excel
	Perspective	Societal
	Time horizon	Remaining lifetime of cohort
	Comparator	No vaccination
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic and probabilistic
Intervention strategy	**Vaccine**	RZV
	Dosing schedule	2-dose
	Age at vaccination	Various: 60yrs, 65yrs, 70yrs, 80yrs
	Coverage rate	First dose: 40%; second dose: 70%
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose efficacy against HZ and PHN 60-69yrs: 90.0%; ≥70yrs: 69.5% RZV 2-dose efficacy against HZ 60-69yrs: 98.4%; ≥70yrs: 97.8%
	Waning	RZV 1-dose Years 1-4: 5.4% p.a. Years 5+: 5.1% p.a. RZV 2-dose <70yrs: 1.0% p.a. in years 1-4; 2.3% p.a. year 5+ ≥70yrs: 3.6% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ ○ outpatient care ○ inpatient care ○ drug prescription ○ therapeutic appliance ○ sick-pay - HZ with PHN ○ outpatient care ○ inpatient care ○ drug prescription ○ therapeutic appliance ○ sick-pay ▪ Vaccination costs
		Measurement and valuation **Direct costs** ▪ Medical costs - EUR cost per HZ case (by age group) (including other non-PHN complications) - EUR cost per PHN case (by age group) (including other non-PHN complications) ▪ Vaccination costs - EUR cost per vaccine dose - EUR cost for administration per dose - EUR cost (weighted average) per adverse event (by age group) based on the incidence of the four adverse event categories and the costs per event, per age group **Indirect costs**

		- vaccine - administration - adverse events o local/general (not requiring medical advice) o GP visit o ER visit o serious **Indirect costs** ▪ Sick leave and co-payments (no further detail reported [2013 study cited as reference]) - HZ - PHN	▪ Sick leave and co-payments (no further detail reported [2013 study cited as reference]) - EUR cost per HZ case (by age group) - EUR cost per PHN case (by age group)
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ Recurrent HZ ▪ PHN ▪ Death **Direct effects of vaccination** ▪ Adverse events	**Measurement and valuation** **Direct effects** ▪ Incidence of initial and recurrent HZ (by age group) ▪ Probability of PHN given HZ (by age group) ▪ HZ-related fatality rate (by age group) **Direct effects of vaccination** ▪ Adverse events - not reported **QALYs** ▪ Baseline utility (by age group) ▪ QALY loss HZ (by age group) ▪ QALY loss PHN ▪ QALY losses due to vaccine-related adverse events considered but data not directly reported
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	N/A	
	Overall societal perspective result	For individuals vaccinated at age: ▪ ≥60yrs, RZV ICER = EUR 37,025/QALY gained versus no vaccination ▪ ≥70yrs, RZV ICER = EUR 43,969/QALY gained versus no vaccination	
Authors conclusions	Starting vaccination with RZV in the German population ≥60yrs old would demonstrate the best value from a public health and economic standpoint.		

Key: CUA – cost-utility analysis; EUR – Euro; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; ZONA – Zoster ecONomic Analysis

General study characteristics	**Author Name, Year of Publication, DOI**	Wolff et al. 2021 DOI: 10.1371/journal.pone.0251644 (study examined the cost effectiveness of varicella and herpes zoster vaccination – only data relating to herpes zoster vaccination extracted)
	Country	Sweden
	Type of Economic Evaluation	CUA
	Population	Hypothetical cohort of people aged 65yrs
	Funding	None
Model characteristics	**Model type**	Age-structured dynamic Markov transmission model (one day time cycle) Health states: 1. Susceptible to HZ 2. Vaccinated against HZ 3. Ill with HZ 4. Recovered from HZ
	Model software	C
	Perspective	1. Health care payer 2. Societal
	Time horizon	20yrs
	Comparator	No vaccination
	Discount rates	3% for costs and outcomes
	Sensitivity analysis	Deterministic
Intervention strategy	**Vaccine**	ZVL (2-dose RZV assessed in sensitivity analysis)
	Dosing schedule	1-dose
	Age at vaccination	65yrs
	Coverage rate	50%
Model input parameters	**Efficacy/effectiveness**	At 65yrs of age: 64% against HZ; 73% against PHN
	Waning	Values unclear: effectiveness reported with an average duration of four years with significant waning after eight years, when only 14% still have immunity
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - primary care consultation for HZ - primary care consultation for PHN - antivirals for HZ - medication for PHN - hospitalisation for HZ - hospitalisation for stroke as a complication of HZ ▪ Vaccination costs - vaccine - vaccine administration **Indirect costs** ▪ Productivity loss - cost for those ill with HZ **Measurement and valuation** **Direct costs** ▪ Medical costs - percentage of HZ cases requiring primary care visit - EUR cost per GP visit - percentage of HZ cases treated with antivirals - EUR cost per pack antivirals - percentage of HZ cases developing PHN - EUR cost per 3 pack gabapentin - number of additional primary care visits required for PHN cases - percentage of HZ cases developing non-PHN complications - EUR weighted average cost for non-PHN complications - percentage of HZ cases requiring hospitalisation - EUR cost for ward admission - EUR cost of doctor per hospital day - EUR cost per hospital day - average length of hospital stay - percentage of HZ cases suffering a stroke within one year of HZ diagnosis - EUR cost per stroke case ▪ Vaccination costs - EUR cost per vaccine dose

			- EUR cost per vaccine dose administration **Indirect costs** ▪ Productivity loss (individuals 0-65yrs old) - average monthly salary + statutory employer's fee - average number of days with production loss
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ PHN ▪ HZ with non-PHN complications	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ ▪ Probability of PHN ▪ Probability of HZ with non-PHN complications **QALYs** ▪ QALY loss HZ (by age)
Economic results	**Type of summary ratio**	ICER	
	Overall health care payer perspective result	ZVL ICER=EUR 267,662/QALY gained versus no vaccination	
	Overall societal perspective result	ZVL ICER=EUR 267,596/QALY gained versus no vaccination	
Authors conclusions	Herpes zoster vaccination with ZVL for the elderly was not cost effective. The health effects of HZ vaccination cannot be considered reasonable in relation to its costs.		

Key: CUA – cost-utility analysis; EUR – Euro; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; ZVL – herpes zoster live vaccine

General study characteristics	**Author Name, Year of Publication, DOI**	You et al. 2018 10.1016/j.vaccine.2018.06.049
	Region, Country	Hong Kong
	Type of Economic Evaluation	CUA
	Population	Healthy males and females aged 50yrs
	Funding	Health and Medical Research Fund (project number 15140432), Food and Health Bureau, The Government of the Hong Kong SAR, China.
Model characteristics	**Model type**	Single cohort Markov model (monthly cycles) Health states: 1. Well 2. HZ 3. PHN 4. HZ related complications (non-PHN) 5. Resolved HZ 6. HZ related death 7. Death due to natural causes
	Model software	Excel and TreeAge
	Perspective	Societal
	Time horizon	50yrs
	Comparator	No vaccination and other ages at vaccination
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way) and probabilistic
Intervention strategy	**Vaccine**	RZV
	Dosing schedule	2-dose
	Age at vaccination	Various: 50yrs, 60yrs, 70yrs
	Coverage rate	First dose: 100%; second dose: 100% (males and females)
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose 88.01% RZV 2-dose Years 1-2: 100%
	Waning	RZV 1-dose 5.07% p.a. RZV 2-dose Year 3 onwards: 3.19% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs - HZ o outpatient care o inpatient care (with and without complications) - PHN ▪ Vaccination costs - vaccine - adverse events o injection site reaction o serious reaction **Indirect costs** ▪ Productivity loss - HZ - PHN
		Measurement and valuation **Direct costs** ▪ Medical costs - Number of clinic visits and USD cost per outpatient HZ case (no complication/PHN) - Length of stay and USD cost per hospitalised HZ case o no complication/PHN o ophthalmicus o secondary skin and soft tissue infection o Ramsay Hunt syndrome o disseminated HZ o central nervous system infection - USD cost per PHN patient (per month) ▪ Vaccination costs - USD cost per vaccine course (2 dose) - USD cost per vaccine injection site reaction - USD cost per vaccine-related serious reaction

		- HZ-associated mortality	
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ PHN ▪ HZ complications - ophthalmicus - secondary skin and soft tissue infection - Ramsay Hunt syndrome - disseminated HZ - central nervous system infection ▪ Hospitalisation ▪ Death **Direct effects of vaccination** ▪ Adverse events - vaccine injection site pain - serious reaction	**Indirect costs** ▪ Productivity loss (estimated using friction cost approach) - labour force participation rate by gender (by age group) - unemployment rate by gender (by age group) - USD median monthly earnings of employed persons by gender (by age group) - friction period assumed as the duration of medical time off **Measurement and valuation** **Direct effects** ▪ Incidence of HZ by gender (by age group) ▪ Percentage of PHN in HZ cases by gender (by age group) ▪ Monthly probabilities of PHN to persist by gender (by age group) ▪ Hospitalisation rate among HZ cases (by age group) ▪ Percentage of complications among hospitalised cases ▪ Mortality rate among hospitalised cases (by age group) **Direct effects of vaccination** ▪ Adverse events - duration of injection-site reaction (days) - probability of serious adverse event within 30 days of vaccination - duration of serious reaction (days) **QALYs** ▪ Baseline utility by gender (by age group) ▪ Utility decrements - HZ at outpatient care - HZ at inpatient care without complication - HZ at inpatient care with complication - PHN - vaccine injection site pain - vaccine-related serious reaction
Economic results	**Type of summary ratio** **Overall payer perspective result** **Overall societal perspective result**	ICER N/A For individuals vaccinated at age: ▪ 50yrs, RZV ICER = USD 64,341/QALY gained versus no vaccination ▪ 60yrs, RZV ICER = USD 47,442/QALY gained versus no vaccination ▪ 70yrs, RZV ICER = USD 46,267/QALY gained versus no vaccination ▪ 60yrs, RZV ICER = USD 49,383/QALY gained versus vaccination at 50yrs ▪ 70yrs, RZV ICER = USD 148,837/QALY gained versus vaccination at 60yrs	
Authors conclusions	Cost effectiveness of each strategy is highly subject to the vaccine cost and WTP threshold per QALY saved.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; USD – United States dollar; WTP – willingness-to-pay

General study characteristics	**Author Name, Year of Publication, DOI**	You et al. 2019 10.1371/journal.pone.0210005
	Region, Country	Hong Kong
	Type of Economic Evaluation	CUA
	Population	Healthy males and females aged ≥50yrs to 80yrs
	Funding	Health and Medical Research Fund (project number 15140432), Food and Health Bureau, The Government of the Hong Kong SAR, China.
Model characteristics	**Model type**	Multi-cohort Markov model (monthly cycles) (31 age cohorts per gender) Health states: 1. Healthy 2. HZ 3. HZ related complication 4. PHN 5. Recovered HZ 6. Recurrent HZ 7. HZ related death 8. Death due to natural causes
	Model software	Excel and TreeAge
	Perspective	Societal
	Time horizon	Until the cohort reaches 100 years old
	Comparator	No vaccination
	Discount rates	3.0% for costs and outcomes
	Sensitivity analysis	Deterministic (one-way) and probabilistic
Intervention strategy	**Dosing schedule**	2-dose RZV
	Vaccine	RZV
	Age at vaccination	Various: yearly ages from 50yrs to 80yrs inclusive for males and females separately
	Coverage rate	First dose: 100%; second dose: 100% (males and females)
Model input parameters	**Efficacy/effectiveness**	RZV 1-dose 88.01% RZV 2-dose Years 1-2: 100%
	Waning	RZV 1-dose 5.07% p.a. RZV 2-dose Year 3 onwards: 3.19% p.a.
	Costs included	**Type of cost** **Direct costs** ▪ Medical costs (including medications, laboratory test, outpatient clinic visits and hospitalisation) - HZ - HZ complications - PHN ▪ Vaccination costs - vaccine - adverse events o injection site reaction **Indirect costs** ▪ Productivity loss
		Measurement and valuation **Direct costs** ▪ Medical costs - Number of outpatient visits and USD cost per outpatient HZ case (no complication or PHN) - Length of stay (days) and USD cost per HZ case for inpatient HZ care with: o no complication or PHN o ophthalmicus o skin and soft tissue infection o Ramsay Hunt syndrome o disseminated HZ o central nervous system infection -USD cost per PHN patient (per month)

		- HZ (inpatient or outpatient)	▪ Vaccination costs - USD cost per vaccine course (2 dose) - USD cost per vaccine injection site reaction (treatment with OTC analgesics and antipyretics) **Indirect costs** ▪ Productivity loss (estimated using friction cost approach) - labour force participation rate by gender (by age group) - unemployment rate by gender (by age group) - USD median monthly earnings of employed persons by gender (by age group) - friction period assumed as the duration of medical time off
	Effects included	**Type of Effects** **Direct effects** ▪ HZ ▪ PHN ▪ HZ complications requiring hospitalistion - ophthalmicus - secondary skin and soft tissue infection - oticus - disseminated HZ - central nervous system infection ▪ Recurrent HZ ▪ Death **Direct effects of vaccination** ▪ Adverse events - vaccine-related injection-site reaction	**Measurement and valuation** **Direct effects** ▪ Incidence of HZ by gender (by age group) ▪ Proportion of HZ cases with PHN by gender (by age group) ▪ Monthly probabilities of PHN to persist by gender (by age group) ▪ Hospitalisation rate among HZ cases (by age group) ▪ HZ complication rate among hospitalised cases (by complication) ▪ HZ-associated mortality rate among hospitalised cases (by age group) **Direct effects of vaccination** ▪ Adverse events - duration of injection-site reaction (days) **QALYs** ▪ Baseline utility by gender (by age group) ▪ Utility decrements - injection-site reaction - outpatient HZ care - inpatient care without HZ complication - inpatient care with HZ complication - PHN
Economic results	**Type of summary ratio**	ICER	
	Overall payer perspective result	N/A	
	Overall societal perspective result	(Figures reported below have been read from graph) For males vaccinated at age: ▪ 50yrs, RZV ICER ~ ranged from USD 37,500 to USD 65,000/QALY gained versus no vaccination, with varying vaccine cost ▪ 60yrs, RZV ICER ~ ranged from USD 27,000 to USD 47,500/QALY gained versus no vaccination, with varying vaccine cost ▪ 70yrs, RZV ICER ~ ranged from USD 27,500 to USD 52,000/QALY gained versus no vaccination, with varying vaccine cost ▪ 80yrs, RZV ICER ~ ranged from USD 43,500 to USD 75,000/QALY gained versus no vaccination, with varying vaccine cost For females vaccinated at age: ▪ 50yrs, RZV ICER ~ ranged from USD 32,000 to USD 56,000/QALY gained versus no vaccination, with varying vaccine cost ▪ 60yrs, RZV ICER ~ ranged from USD 25,000 to USD 45,000/QALY gained versus no vaccination, with varying vaccine cost ▪ 70yrs, RZV ICER ~ ranged from USD 24,000 to USD 44,000/QALY gained versus no vaccination, with varying vaccine cost ▪ 80yrs, RZV ICER ~ ranged from USD 35,000 to USD 60,000/QALY gained versus no vaccination, with varying vaccine cost	
Authors conclusions	RZV vaccine is more likely to be cost-effective for males and females aged between 60-70 years than the extreme age groups (<60 years and >70 years) in Hong Kong. The age range for cost-effective acceptance of RZV vaccine appears to be broader in females than males given the same vaccine cost and willingness-to-pay threshold.		

Key: CUA – cost-utility analysis; HZ – herpes zoster; ICER – incremental cost-effectiveness ratio; PHN – post-herpetic neuralgia; QALY – quality-adjusted life-year; RZV – recombinant zoster vaccine; USD – United States dollar

Appendix C

Appendix C 6.1 Economic model parameters

Parameter description	Mean	Lower CI (95%)	Upper CI (95%)	Distribution	Source
Epi parameters					
Risk of HZ by age	Characterised by equations detailed in Section 6.2.9 of the report.				Kawai 2014,[6]
Risk of PHN by age					Alicino 2017,[119] Cebrian-Cuenca 2011,[284] Gauthier 2009,[123] Helgason 2000,[285] Munoz-Quiles 2018,[124] Opstelten 2002,[125] Yang 2019,[286]
Resource use parameters					
Probability of hospitalisation					
Probability of hospitalisation HZ [Age group 1]	1.0%	0.5%	1.5%	Beta	Hospital Inpatient Enquiry (HIPE) System[306]
Probability of hospitalisation HZ [Age group 2]	1.0%	0.5%	1.5%	Beta	
Probability of hospitalisation HZ [Age group 3]	1.5%	0.9%	2.1%	Beta	
Probability of hospitalisation HZ [Age group 4]	1.6%	1.1%	2.3%	Beta	
Probability of hospitalisation HZ [Age group 5]	2.0%	1.4%	2.7%	Beta	
Probability of hospitalisation HZ [Age group 6]	2.2%	1.5%	3.0%	Beta	
Probability of hospitalisation HZ [Age group 7]	4.5%	3.3%	5.9%	Beta	
Probability of hospitalisation HZ [Age group 8]	4.5%	3.3%	5.9%	Beta	
Probability of medical card					
Probability of medical card [Age group 1]	0.257	25.7%	25.7%	Fixed	PCRS Eligibility Report Nov 2023,[305]
Probability of medical card [Age group 2]	0.309	30.9%	30.9%	Fixed	
Probability of medical card [Age group 3]	0.309	30.9%	30.9%	Fixed	

Parameter description	Mean	Lower CI (95%)	Upper CI (95%)	Distribution	Source
Probability of medical card [Age group 4]	0.388	38.8%	38.8%	Fixed	
Probability of medical card [Age group 5]	0.572	57.2%	57.2%	Fixed	
Probability of medical card [Age group 6]	0.769	76.9%	76.9%	Fixed	
Probability of medical card [Age group 7]	0.769	76.9%	76.9%	Fixed	
Probability of medical card [Age group 8]	0.769	76.9%	76.9%	Fixed	
Probability of GP visit card					
Probability of GP visit card [Age group 1]	0.031	3.1%	3.1%	Fixed	PCRS Eligibility Report Nov 2023,[305]
Probability of GP visit card [Age group 2]	0.025	2.5%	2.5%	Fixed	
Probability of GP visit card [Age group 3]	0.025	2.5%	2.5%	Fixed	
Probability of GP visit card [Age group 4]	0.028	2.8%	2.8%	Fixed	
Probability of GP visit card [Age group 5]	0.349	34.9%	34.9%	Fixed	
Probability of GP visit card [Age group 6]	0.231	23.1%	23.1%	Fixed	
Probability of GP visit card [Age group 7]	0.231	23.1%	23.1%	Fixed	
Probability of GP visit card [Age group 8]	0.231	23.1%	23.1%	Fixed	
Cost parameters					
Cost of hospitalisation					
Cost of hospitalisation for HZ [Age group 1]	€5,870	€4,755	€7,101	Gamma	HPO ABF Admitted Patient Price List,[307]
Cost of hospitalisation for HZ [Age group 2]	€6,134	€4,969	€7,420	Gamma	
Cost of hospitalisation for HZ [Age group 3]	€5,477	€4,436	€6,625	Gamma	
Cost of hospitalisation for HZ [Age group 4]	€6,082	€4,927	€7,357	Gamma	
Cost of hospitalisation for HZ [Age group 5]	€6,137	€4,971	€7,423	Gamma	
Cost of hospitalisation for HZ [Age group 6]	€6,167	€4,995	€7,459	Gamma	
Cost of hospitalisation for HZ [Age group 7]	€5,930	€4,803	€7,173	Gamma	
Cost of hospitalisation for HZ [Age group 8]	€5,917	€4,793	€7,158	Gamma	
Cost of GP					
Cost of GP visits for acute HZ [Age group 1] (total)	€117.65	€95.30	€142.32	Gamma	Crosbie et al. 2018,[108]
Cost of GP visits for acute HZ [Age group 2] (total)	€117.65	€95.30	€142.32	Gamma	
Cost of GP visits for acute HZ [Age group 3] (total)	€117.65	€95.30	€142.32	Gamma	
Cost of GP visits for acute HZ [Age group 4] (total)	€117.65	€95.30	€142.32	Gamma	

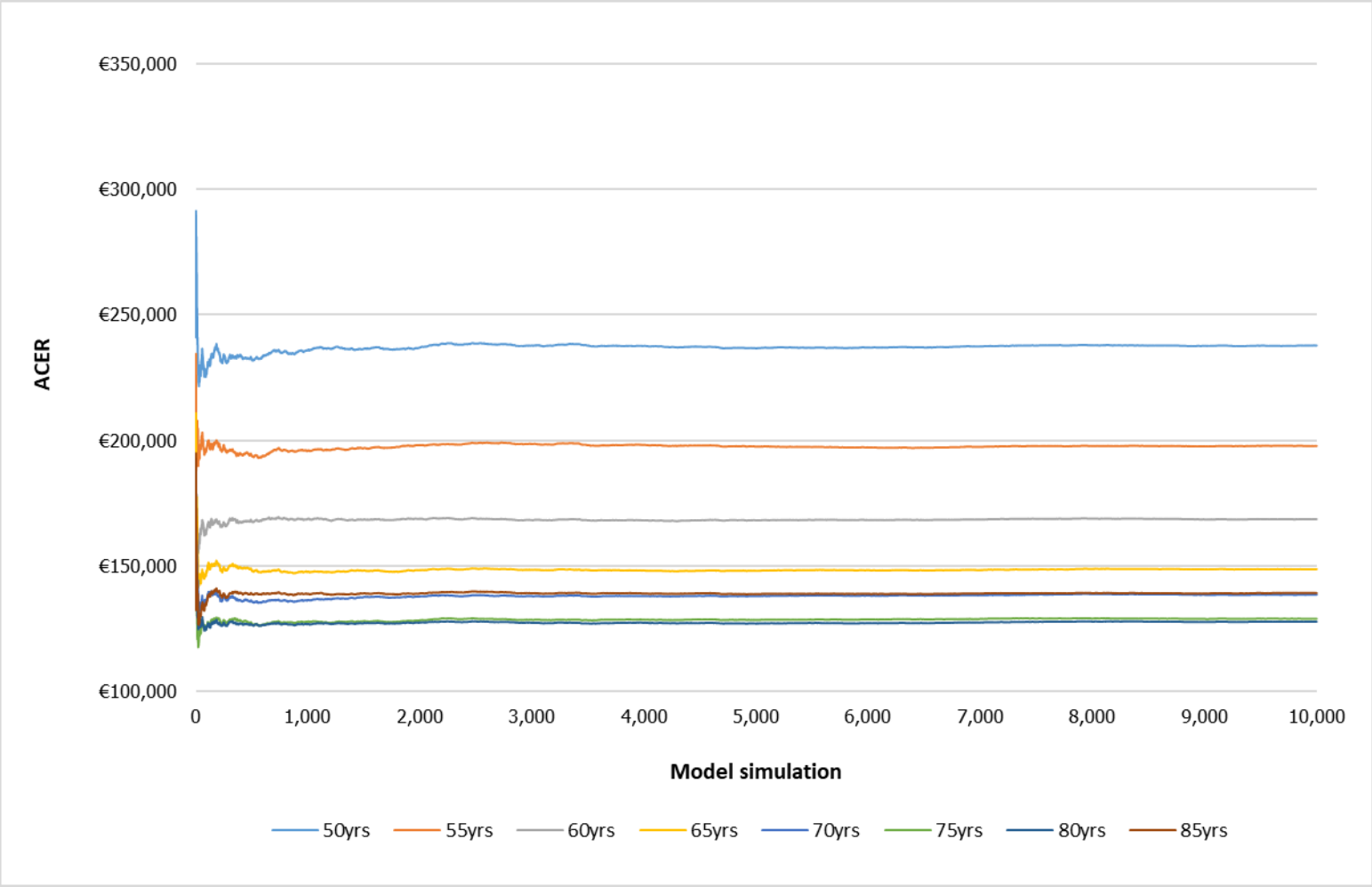
Parameter description	Mean	Lower CI (95%)	Upper CI (95%)	Distribution	Source
Cost of GP visits for acute HZ [Age group 5] (total)	€117.65	€95.30	€142.32	Gamma	
Cost of GP visits for acute HZ [Age group 6] (total)	€117.65	€95.30	€142.32	Gamma	
Cost of GP visits for acute HZ [Age group 7] (total)	€117.65	€95.30	€142.32	Gamma	
Cost of GP visits for acute HZ [Age group 8] (total)	€117.65	€95.30	€142.32	Gamma	
Cost of GP visits for PHN [Age group 1] (monthly)	€25.57	€20.71	€30.93	Gamma	Calculated based on duration of PHN and Crosbie et al. 2018,[108]
Cost of GP visits for PHN [Age group 2] (monthly)	€24.69	€20.00	€29.87	Gamma	
Cost of GP visits for PHN [Age group 3] (monthly)	€23.81	€19.29	€28.80	Gamma	
Cost of GP visits for PHN [Age group 4] (monthly)	€22.93	€18.57	€27.74	Gamma	
Cost of GP visits for PHN [Age group 5] (monthly)	€22.05	€17.86	€26.67	Gamma	
Cost of GP visits for PHN [Age group 6] (monthly)	€21.17	€17.15	€25.61	Gamma	
Cost of GP visits for PHN [Age group 7] (monthly)	€20.29	€16.44	€24.55	Gamma	
Cost of GP visits for PHN [Age group 8] (monthly)	€18.51	€14.99	€22.39	Gamma	
Cost of medication					
Cost of medication for acute HZ [Age group 1] (total)	€81.51	€66.03	€98.60	Gamma	Crosbie et al. 2018,[108]
Cost of medication for acute HZ [Age group 2] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for acute HZ [Age group 3] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for acute HZ [Age group 4] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for acute HZ [Age group 5] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for acute HZ [Age group 6] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for acute HZ [Age group 7] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for acute HZ [Age group 8] (total)	€81.51	€66.03	€98.60	Gamma	
Cost of medication for PHN [Age group 1] (monthly)	€19.92	€16.14	€24.10	Gamma	Calculated based on duration of PHN and Crosbie et al. 2018,[108]
Cost of medication for PHN [Age group 2] (monthly)	€19.66	€15.93	€23.78	Gamma	
Cost of medication for PHN [Age group 3] (monthly)	€19.42	€15.73	€23.49	Gamma	
Cost of medication for PHN [Age group 4] (monthly)	€19.20	€15.55	€23.23	Gamma	
Cost of medication for PHN [Age group 5] (monthly)	€19.00	€15.39	€22.99	Gamma	
Cost of medication for PHN [Age group 6] (monthly)	€18.83	€15.25	€22.78	Gamma	
Cost of medication for PHN [Age group 7] (monthly)	€18.69	€15.14	€22.60	Gamma	
Cost of medication for PHN [Age group 8] (monthly)	€18.49	€14.98	€22.37	Gamma	

Parameter description	Mean	Lower CI (95%)	Upper CI (95%)	Distribution	Source
Cost of Productivity Loss					
Cost of Productivity Loss [Age group 1] (daily)	160.14	129.72	193.72	Gamma	CSO Labour Force Survey and Earnings Analysis using Administrative Data Sources,[309, 310]
Cost of Productivity Loss [Age group 2] (daily)	160.14	129.72	193.72	Gamma	
Cost of Productivity Loss [Age group 3] (daily)	124.14	100.56	150.17	Gamma	
Cost of Productivity Loss [Age group 4] (daily)	124.14	100.56	150.17	Gamma	
Cost of Productivity Loss [Age group 5] (daily)	124.14	100.56	150.17	Gamma	
Cost of Productivity Loss [Age group 6] (daily)	124.14	100.56	150.17	Gamma	
Cost of Productivity Loss [Age group 7] (daily)	124.14	100.56	150.17	Gamma	
Cost of Productivity Loss [Age group 8] (daily)	124.14	100.56	150.17	Gamma	
Duration parameters					
Mean Duration of PHN					
Duration of PHN [Age group 1] (months)	4.9	4.0	6.1	Gamma	Calculated based on estimated probability (by fitting a line to international data) of moving from PHN to Recovered
Duration of PHN [Age group 2] (months)	5.1	4.1	6.5	Gamma	
Duration of PHN [Age group 3] (months)	5.3	4.2	6.9	Gamma	
Duration of PHN [Age group 4] (months)	5.5	4.3	7.3	Gamma	
Duration of PHN [Age group 5] (months)	5.7	4.4	7.9	Gamma	
Duration of PHN [Age group 6] (months)	5.9	4.5	8.4	Gamma	
Duration of PHN [Age group 7] (months)	6.2	4.6	9.1	Gamma	
Duration of PHN [Age group 8] (months)	6.8	4.8	10.8	Gamma	
Duration of Productivity Loss HZ					
Duration of Productivity Loss HZ [Age group 1] (days)	4	3	5	Gamma	Drolet et al. 2012,[153] Scott et al. 2006,[154] Singhal et al. 2011,[155]
Duration of Productivity Loss HZ [Age group 2] (days)	4	3	5	Gamma	
Duration of Productivity Loss HZ [Age group 3] (days)	4	3	5	Gamma	
Duration of Productivity Loss HZ [Age group 4] (days)	4	3	5	Gamma	
Duration of Productivity Loss HZ [Age group 5] (days)	4	3	5	Gamma	
Duration of Productivity Loss HZ [Age group 6] (days)	4	3	5	Gamma	
Duration of Productivity Loss HZ [Age group 7] (days)	4	3	5	Gamma	
Duration of Productivity Loss HZ [Age group 8] (days)	4	3	5	Gamma	
Utility parameters					

Parameter description	Mean	Lower CI (95%)	Upper CI (95%)	Distribution	Source
Utility baseline					
Utility baseline [Age group 1]	0.91	0.91	0.91	Beta	Hobbins et al. 2018,[141]
Utility baseline [Age group 2]	0.90	0.90	0.90	Beta	
Utility baseline [Age group 3]	0.90	0.90	0.90	Beta	
Utility baseline [Age group 4]	0.88	0.88	0.88	Beta	
Utility baseline [Age group 5]	0.88	0.88	0.88	Beta	
Utility baseline [Age group 6]	0.84	0.84	0.84	Beta	
Utility baseline [Age group 7]	0.84	0.84	0.84	Beta	
Utility baseline [Age group 8]	0.84	0.84	0.84	Beta	
Utility HZ					
Utility HZ [Age group 1]	0.7990	0.7516	0.8421	Beta	Drolet et al. 2010,[139] Tsai et al. 2015,[303] Curran et al. 2018,[138] Curran et al. 2019,[241] Matthews et al. 2019,[300] Diez-Domingo et al. 2021,[137] Mizukami et al. 2018,[140] Gater et al. 2014,[299] Song et al. 2014,[301] Toniolo-Neto et al. 2018,[302]
Utility HZ [Age group 2]	0.7880	0.7397	0.8320	Beta	
Utility HZ [Age group 3]	0.7770	0.7280	0.8219	Beta	
Utility HZ [Age group 4]	0.7660	0.7162	0.8118	Beta	
Utility HZ [Age group 5]	0.7550	0.7045	0.8016	Beta	
Utility HZ [Age group 6]	0.7440	0.6929	0.7914	Beta	
Utility HZ [Age group 7]	0.7330	0.6813	0.7812	Beta	
Utility HZ [Age group 8]	0.7210	0.6686	0.7698	Beta	
Utility PHN					
Utility PHN [Age group 1]	0.7920	0.7444	0.8359	Beta	Drolet et al. 2010,[139] Diez-Domingo et al. 2021,[137] Mizukami et al. 2018,[140] Curran et al. 2018,[138]
Utility PHN [Age group 2]	0.7650	0.7150	0.8107	Beta	
Utility PHN [Age group 3]	0.7370	0.6858	0.7852	Beta	
Utility PHN [Age group 4]	0.7100	0.6569	0.7594	Beta	
Utility PHN [Age group 5]	0.6820	0.6283	0.7334	Beta	
Utility PHN [Age group 6]	0.6550	0.5998	0.7072	Beta	
Utility PHN [Age group 7]	0.6270	0.5716	0.6808	Beta	
Utility PHN [Age group 8]	0.5970	0.5408	0.6515	Beta	
Vaccination parameters					

Parameter description	Mean	Lower CI (95%)	Upper CI (95%)	Distribution	Source
Cost of vaccine (per dose)	151.00	122.32	182.66	Gamma	Assumed
Cost of vaccine administration public (per dose)	25.00	20.25	30.24	Gamma	HSE,[311]
Cost of cold chain service (proportion of vaccine procurement cost)	3.90%	3.00%	5.00%	Fixed	National Immunisation Office,[312]
Cost of education and communication (proportion of vaccine procurement cost)	1.50%	0.50%	2.50%	Fixed	
Relative risk of HZ vaccinated (1 - vaccine effectiveness)	29.8%	25.6%	34.0%	Normal	Chapter 4 Clinical Efficacy & Safety
Risk difference with waning immunity (per month)	0.21%	0.15%	0.27%	Normal	Chapter 4 Clinical Efficacy & Safety
Relative risk of PHN with vaccination	38.6%	12.5%	64.7%	Normal	Chapter 4 Clinical Efficacy & Safety
Probability vaccine-related adverse event (grade 3)	14.0%	8.0%	21.4%	Beta	Chapter 4 Clinical Efficacy & Safety
Probability GP visit for vaccine-related adverse event (grade 3)	100%	100%	100%	Beta	Assumed
Coverage rate_budget impact analysis	50%	30%	70%	Fixed	Assumed
Other parameters					
Discount rate					
Discount rate costs	4%	3%	5%	Fixed	HIQA 2020. Guidelines for the Economic Evaluation of Health Technologies in Ireland,[272]
Discount rate outcomes	4%	3%	5%	Fixed	
Employment rate					
Employment rate [Age group 1]	83%	83%	83%	Fixed	CSO Labour Force Survey Quarter 2 2023,[309]
Employment rate [Age group 2]	75%	75%	75%	Fixed	
Employment rate [Age group 3]	61%	61%	61%	Fixed	
Employment rate [Age group 4]	25%	25%	25%	Fixed	
Employment rate [Age group 5]	15%	15%	15%	Fixed	
Employment rate [Age group 6]	10%	10%	10%	Fixed	
Employment rate [Age group 7]	0%	0%	0%	Fixed	
Employment rate [Age group 8]	0%	0%	0%	Fixed	
Other costs					
Cost of GP visit_public patient	€51.23	€41.50	€61.97	Gamma	Smith et al. 2021,[371]
Cost of GP visit_private patient	€61.48	€49.80	€74.37	Fixed	Assumed 6/5ths of public cost

Appendix C 6.2 Model convergence by age at herpes zoster vaccination



Key: ACER – average cost-effectiveness ratio

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