Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

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

## DRAFT Health Technology Assessment for Public Consultation

**Publication date: 20 April 2023**

# About the Health Information and Quality Authority

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

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

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

# Foreword

Varicella is a common, highly infectious, but vaccine-preventable, disease caused by the varicella zoster virus (VZV). VZV is associated with two distinct clinical syndromes, varicella, commonly known as chickenpox, and herpes zoster, commonly known as shingles. Primary infection with VZV results in varicella, after which the virus becomes latent in the body's nervous system. The virus may reactivate after a period, sometimes several decades later, resulting in herpes zoster. Almost everyone exposed to VZV who is not immune, through prior infection or vaccination, will develop varicella. Approximately one in three people who have had varicella will eventually develop herpes zoster.

Varicella mainly affects children and currently in Ireland, approximately 55,000 people develop the disease each year. Varicella is a highly infectious disease with one case of varicella potentially infecting 10-12 susceptible others. Varicella is typically a mild self-limiting disease. However, varicella can lead to serious complications requiring hospitalisation in healthy as well as immunocompromised individuals.

A vaccine for chickenpox was developed in the 1970s. Currently, nine EU/EEA countries have funded universal childhood varicella vaccination programmes as well as Australia, Canada, New Zealand and the USA. In Ireland, varicella vaccination is not currently included in the childhood immunisation programme provided by the Health Service Executive (HSE), although the vaccine is available to purchase privately if parents or guardian want their child vaccinated. The purpose of this health technology assessment (HTA) was to establish the clinical effectiveness, cost effectiveness and budget impact of an expansion of the childhood immunisation schedule in Ireland to include varicella (chickenpox) vaccination.

Work on the health technology assessment (HTA) was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group (EAG) 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 draft report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

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# Expert advisory group membership

The membership of the EAG was as follows:

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**Key:** *Alternate for Dr Colette Bonner, Deputy Chief Medical Officer, Department of Health
#Joined the EAG after the second meeting.

# Members of the Evaluation Team

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# 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) for their time and advice. We would also like to express our gratitude to the Health Protection Surveillance Centre and the Healthcare Pricing Office of the Health Service Executive for sharing and advising on data used in chapters 3 and 7, respectively.

# Executive summary

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The aim of the HTA was to establish the clinical effectiveness, cost-effectiveness and budget impact of an expansion of the childhood immunisation schedule in Ireland to include varicella (chickenpox) vaccination. This HTA considered the following domains:

- description of technology
- epidemiology and burden of disease
- clinical effectiveness
- safety
- review of methodology of economic modelling of varicella vaccination
- economic evaluation
- organisational issues
- ethical and social issues.

# 1 Background

Following a request from the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a HTA in relation to an expansion of the childhood immunisation schedule to include varicella vaccination. The request was supported by the National Immunisation Advisory Committee (NIAC).

# 2 Description of the technology

Varicella is a common, highly infectious, but vaccine-preventable, disease caused by the varicella zoster virus (VZV). Approximately 96% of those who are exposed to the VZV and are not immune, through prior infection or vaccination, will develop the disease. Varicella mainly affects children and the annual incidence in EU/EEA countries typically approximates the annual birth cohort; the total number of births in Ireland in 2021 was approximately 58,500.

Four vaccines are licensed and marketed in Europe to prevent primary VZV infection, of which one is currently marketed for use in Ireland; the monovalent vaccines

Varivax® (marketed in Ireland and available to purchase privately) and Varilrix® and the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines, ProQuad® and Priorix-Tetra®. The vaccines differ in terms of recommended dosing intervals, interchangeability and co-administration with other vaccines.

The USA was the first country to license the monovalent vaccine for universal routine vaccination of persons aged at least 12 months in 1995, while Germany was the first country in Europe to recommend nationwide universal childhood varicella vaccination in 2004. Approval for the quadrivalent MMRV vaccine was granted in 2005 in the USA and in 2006 in Europe. Since the mid-1990s, the number of countries that have introduced funded universal childhood varicella vaccination programmes has grown and currently includes nine EU/EEA countries as well as Australia, Canada and New Zealand among others. Established varicella vaccination programmes are heterogeneous and differ according to the recommended dosing schedule, type of vaccine(s) recommended, age at which the first dose is recommended and the interval between doses where a two-dose schedule is in place.

# 3 Epidemiology and burden of disease

Varicella is a highly infectious disease and estimates of the basic reproduction number indicate a range of 10-12, meaning that one case of varicella potentially infects 10-12 susceptible others. After VZV infection, most people develop immunity for the remainder of their lives.

The annual incidence rate of VZV primary infection (derived from seroprevalence data) in Ireland has been estimated at:

- 11,954 per 100,000 population in those aged less than five years,
- 6,434 per 100,000 population in those aged five to nine years, and
- 76 per 100,000 population in those aged 10 to 14 years.

Seroprevalence of antibodies against varicella in those aged less than 15 years in Ireland has been estimated at 92.3%, reaching 95.3% in those aged less than 65 years.

Varicella is typically a mild self-limiting disease. However, varicella can lead to serious complications and in very rare cases, death in healthy as well as immunocompromised individuals. Serious complications include bacterial superinfections of skin and soft tissue (typically Group A streptococcus) with and without sepsis, as well as neurological, gastrointestinal, hepatic and haematological complications requiring hospitalisation. A total of 2,717 hospital admissions with a

principal diagnosis of varicella (96.3% had no underlying condition) were reported over a 12 year period from 2005 to 2016, with an average of 226 admissions per annum, and infants and young children comprising the majority of admissions. It is recognised that there are also hospital admissions for children with complications from recent varicella infection, but reliable data on these cases are not routinely available.

Primary infection with VZV results in varicella, after which the virus becomes latent in the body's nervous system. The virus may reactivate after a period, sometimes several decades later, resulting in herpes zoster (shingles). The lifetime risk of developing herpes zoster is approximately 30%. Morbidity associated with herpes zoster increases with age and the most common complication is post-herpetic neuralgia; persistent pain (for more than 90 days after onset) in the area of the rash with the potential to cause significant reductions in quality of life, activity, mood and sleep.

Although limited research has been published examining the total economic burden of VZV in Ireland, estimates suggest that the burden, including both direct and indirect costs, is likely to be considerable.

# 4 Clinical effectiveness

A number of systematic reviews assessing the efficacy and effectiveness of varicella vaccines have been published over the last 40 years. Early reviews assessed the monovalent vaccine and a one-dose schedule, while more recent reviews assessed both the monovalent and quadrivalent MMRV vaccines and one- and two-dose schedules. An overview of reviews was undertaken to assess the current systematic review evidence of the clinical efficacy and effectiveness alternative varicella vaccination strategies.

In total, 20 systematic reviews incorporating 15 randomised controlled trials and 206 other primary studies/reviews were included in the overview of reviews; 17 reviews assessed the efficacy/effectiveness of one-dose strategies and 10 reviews assessed the efficacy/effectiveness of two-dose strategies.

Based on estimates from reviews that conducted a meta-analysis, one-dose vaccination strategies (both monovalent and quadrivalent varicella vaccine types) are effective in preventing varicella of any severity, although effectiveness varied considerably, ranging from 67% efficacy up to 10 years after vaccination, to 88% effectiveness (follow-up period not reported). In outbreak settings specifically, one-dose effectiveness ranged from 54% nine to 10 years after vaccination to 98% at less than 3 years after vaccination. The evidence also suggests that one-dose vaccination strategies are highly effective against moderate to severe varicella with

effectiveness estimates ranging from 90% to 100%. Evidence of waning immunity was most notable against varicella of any severity for one-dose strategies.

Estimates of the effectiveness of two-dose varicella vaccination strategies (from reviews that conducted a meta-analysis) to prevent varicella of any severity were less variable, ranging from 87% to 95%, with similar estimates for outbreak settings. The evidence on the efficacy/effectiveness of two-dose vaccination in preventing moderate and severe varicella was limited to a single review that reported 99% efficacy at ten years follow-up post vaccination.

A quality appraisal of included reviews was conducted. The main issues identified related to methodological flaws at the systematic review level rather than primary study level, and lack of detail in the reporting of reviews. It should be noted that the reviews were published over a long time span during which methodology for systematic reviews has developed and been increasingly formalised. The continued development and application of reporting guidelines also mean that more recent reviews tend to have higher quality ratings.

Overall, there is clear and consistent evidence that vaccination is very effective at reducing varicella.

# 5 Safety

A number of systematic reviews assessing the safety of varicella vaccination have also been published over the last 40 years. Early reviews assessed the monovalent vaccine and one-dose, while more recent reviews assessed both the monovalent and quadrivalent MMRV vaccines and one- and two-doses. An overview of reviews was undertaken to establish the clinical safety of potential varicella vaccination strategies by synthesising the evidence available from relevant systematic reviews that have been published to date.

In total, 17 systematic reviews were included in the overview of reviews; six assessed the safety of one-dose varicella vaccination, 4 assessed the safety of two-dose vaccination, 2 assessed two- versus one-dose vaccination and 14 reviews did not specify the number of vaccine doses.

The evidence suggests that mild local and systemic reactions, such as fever and rash, are relatively common, and while febrile seizures are possible adverse effects of both the monovalent and quadrivalent MMRV vaccine, serious adverse events are rare. The limited evidence on the co-administration of the varicella vaccine with other vaccines suggests that co-administration does not compromise the safety of the vaccines. The potential harms associated with varicella vaccination must be

considered in light of the clinical benefits associated with reduced rates of varicella zoster virus infection and incidence of varicella disease.

While the analysis by vaccine type and dosing strategy was restricted due to lack of detail in reporting of the systematic reviews, overall, there was clear and consistent evidence from a substantial evidence base, comprising 34 RCTs and 62 other primary studies/reviews, that that both monovalent and quadrivalent varicella vaccination are safe.

# 6 Review of methodology of economic modelling of varicella vaccination

The most recent systematic review of economic modelling studies of routine varicella vaccination in high income countries was published in 2015. To establish and assess the most up to date international evidence on the approaches taken to the economic modelling of universal childhood varicella vaccination, and to inform the development of a de novo economic model for Ireland, a rapid review of studies published since 2015 was undertaken.

Nine additional studies were identified in the rapid review, eight of which were conducted for European countries. Five studies were funded by industry, two by government agencies, one by a research body, and one declared no funding.

Eight studies employed dynamic transmission modelling, using a series of ordinary differential equations, to estimate the impact of varicella vaccination on VZV transmission, while one used a dynamic Markov model. This compared with the use of dynamic transmission modelling in 13 of 23 studies in the 2015 systematic review. Seven studies took account of the exogenous boosting theory and modelled the impact of varicella vaccination on incidence of herpes zoster. Most studies included in the earlier systematic review were reported to have ignored the relationship between varicella and herpes zoster. Similar to the earlier review, the analysis was conducted from both the healthcare payer and societal perspectives in the majority of studies (n=7), with the tax payer and societal perspectives adopted in one study each.

A critical appraisal of included studies was also undertaken. While overall the appraisal did not raise major concerns with the quality of included studies, there were some concerns with regard to structural assumptions, 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.

The rapid review identified several notable modelling features for consideration when developing economic models of routine varicella vaccination, all of which were

considered for inclusion when developing a de novo economic model of varicella vaccination for Ireland.

# 7 Economic evaluation

A dynamic transmission model was developed to model the transmission of VZV in Ireland and the incidence of varicella and herpes zoster diseases both before and after the introduction of a universal childhood varicella vaccination programme. The epidemiological outputs from the dynamic transmission model were subsequently used in an economic model developed to estimate the cost effectiveness and budget impact of a universal childhood varicella vaccination programme compared with no vaccination.

Three alternative vaccination strategies were analysed:

- one-dose administered at 12 months
- two-dose short interval administered at 12 months and 15 months
- two-dose long interval administered at 12 months and five years

The estimated effectiveness of one- and two-dose vaccination strategies were obtained from the overview of reviews of the clinical effectiveness of varicella vaccination.

From the payer perspective, a one-dose strategy was the least costly of all three strategies. The incremental cost-effectiveness ratio (ICER) for a one-dose strategy, compared with no vaccination, was estimated at €8,712 per quality-adjusted life year (QALY) gained. In the deterministic sensitivity analysis, the one-dose strategy was considered cost effective at a willingness to pay (WTP) threshold of €20,000/QALY gained for all parameters tested. The two-dose long interval strategy was the next least costly option and compared with one-dose vaccination, the ICERwas estimated at €45,090 per QALY gained. The two-dose short interval strategy was the most costly and most effective strategy and compared with the one-dose strategy, the ICER was estimated at €44,106/QALY gained. The sensitivity analysis highlighted the uncertainty associated with the ICERs for both two-dose strategies and their cost-effectiveness at a WTP threshold of €45,000/QALY gained.

The results of the univariate sensitivity analysis demonstrated that the cost-effectiveness results for the one-dose strategy, relative to no vaccination, were most sensitive to changes in the uptake rate and the cost of the vaccine. Similarly, the results of two-dose cost-effectiveness, relative to one-dose, were most sensitive to changes in the uptake rate, the cost of the vaccine and the QALY loss associated with varicella. When comparing the two-dose strategies, the cost-effectiveness of

the two-dose short interval strategy was most sensitive to changes in waning immunity associated with one dose and the force of infection in vaccinated individuals.

From a societal perspective, all three vaccination strategies dominated the no vaccination scenario, being less costly and more effective, with the two-dose short interval strategy dominant over all others.

The budget impact over five years was estimated at €13.1 million, €28.1 million and €16.1 million for the one-dose, two-dose short interval, and two-dose long interval strategies respectively. This assumes an annual eligible cohort of 60,000 children per annum. The incremental costs associated with the introduction of a varicella vaccination programme include associated cost savings, mainly comprising the costs associated with a reduction in hospitalisation for varicella. The five-year budget impact was most sensitive to the changes in the cost of the vaccine. The lower budget impact for the two-dose long interval strategy, compared with the two-dose short interval strategy, reflects the fact that only one birth cohort will have completed the two-dose schedule within the five year time horizon of the BIA. From year five onwards, the difference in cost between the two-dose strategies should only reflect the difference in cost (if any) between administering the vaccine in the GP practice setting and the school setting.

This modelling study is subject to a number of limitations. As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values. There are a number of aspects of the epidemiology of VZV infection that are not fully understood and therefore key model parameters, including the duration of cell-mediated immunity following primary VZV infection, are highly uncertain. Additionally, the exogenous boosting theory is poorly understood, much debated and the magnitude of the effect, if it exists, is unknown. While probabilistic sensitivity analysis (PSA) is the preferred approach for exploring uncertainty arising from parameter imprecision, a full PSA was not possible due to the complexity of the model which created a significant computational burden.

# 8 Organisational issues

Each of the three varicella vaccination regimens assessed will give rise to different organisational implications. A one-dose regimen will take place as part of the existing childhood immunisation programme and may result in the 12 month visit being prolonged by the addition of varicella vaccination. In addition to leveraging off the current 12 month immunisation visit, a two-dose short interval regimen will create a new immunisation visit at 15 months. This regimen will therefore require an additional GP visit, placing a burden on primary care as well as parents and

guardians. A two-dose long interval regimen will leverage off the existing 12 month GP visit and the schools-based immunisation visit for four to five year olds, but in both instances may result in additional time required for vaccination.

An information campaign for parents will be an important component of any change to the national immunisation schedule, to educate parents, 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 childhood vaccines as part of the immunisation programme.

# 9 Ethical and social issues

The ethical issues raised around a technology must be assessed in relation to the prevalent social and moral norms relevant to the technology. 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.

The purpose of vaccination is very clear and is to prevent or reduce the spread of infectious disease. In terms of the benefits-harm balance of varicella vaccination, there is clear and consistent evidence that it is very effective at reducing incidence and the risk of severe disease. Almost everyone who is not vaccinated against varicella will contract the disease over their lifetime, the majority before the age of ten years. Additionally, the lifetime risk of subsequently developing herpes zoster is approximately 30%. As such, and unusually for an immunisation programme, most people who therefore get vaccinated against varicella will personally benefit through avoiding infection. The varicella vaccine is also considered safe. While mild local and systemic reactions, such as fever and rash, are relatively common, serious adverse events are rare. Varicella breakthrough is more likely in one-dose versus two-dose strategies, therefore it is possible that the one-dose regimen may shift the age distribution of varicella infection in unvaccinated people. This potentially creates a risk because varicella can be more severe for older children and adults.

The vaccination programme being assessed involves administration of the varicella vaccine to children. It is therefore the responsibility of parents and guardians to provide informed consent. In giving consent, and exercising autonomy with regard to that decision, it is important that parents and guardians fully understand the benefits and harms of vaccination.

If a high proportion of eligible children avail of varicella vaccination, it will confer some degree of herd immunity within the population. Such protection may be particularly beneficial for those who are immunocompromised and ineligible for the vaccine.

The healthcare budget is finite and policy makers have a duty to ensure that healthcare resources are allocated fairly. The addition of varicella vaccination to the childhood immunisation schedule will require annual funding and could potentially impact the provision of other health technologies within the healthcare system. It will create demand for primary care resources that could result in displaced care. Therefore decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity cost of new investments are considered.

# 10 Conclusions

Varicella is a common, highly infectious, but vaccine-preventable, disease, mainly affecting children. Although typically a mild disease, serious complications can and do occur. Over time, those who have recovered from varicella become susceptible to herpes zoster and have an estimated lifetime risk of 30% of developing the disease. Although limited research has been published examining the total economic burden of varicella in Ireland, estimates suggest that the burden, including both direct and indirect costs, is likely to be considerable.

Varicella vaccination is highly effective and safe in preventing varicella, including severe disease and its complications. Based on an economic evaluation of three potential universal childhood varicella vaccination strategies in Ireland, a one-dose strategy is considered a cost-effective intervention, compared with no vaccination, from the payer perspective. From a societal perspective, and compared with no vaccination, a two-dose short interval strategy generates the greatest benefits and cost savings of the three potential strategies.

Implementation of a varicella vaccination programme would give rise to organisational implications that differ depending on the vaccination strategy. Provision of a universal childhood varicella vaccination programme would be associated with ongoing programme costs. However, it would also result in costs averted due to a reduction in the burden of varicella and herpes zoster on the healthcare system, both in the short- and long-term, owing to reductions in primary care consultations and hospitalisations for severe disease and complications. Additionally, from a societal perspective, varicella vaccination would reduce the significant productivity losses that arise for parents and caregivers when children with varicella, of any severity, require care.

If a decision is made to expand the childhood immunisation schedule to include varicella vaccination, the potential impacts on the existing immunisation schedule (both GP- and school-based), and the overall provision of primary care services must be considered. Additionally, an information campaign for parents, supported by an educational programme for frontline healthcare workers will be key components of any change to the national immunisation schedule.

While a one-dose strategy is sufficient to reduce severe morbidity from varicella, a two-dose strategy is required to further reduce the number of cases and outbreaks. In the event that the childhood immunisation programme is expanded to include varicella vaccination, the choice of strategy should be influenced by the specific aim of a varicella vaccination programme.

# Plain language summary

Chickenpox is caused by a virus. It is very common among children, but it can happen at any age. About 55,000 people get chickenpox in Ireland every year. The chickenpox spots can be very itchy and uncomfortable and the person can feel sick for a few days. It normally gets better without having to go to a doctor, but a very small number of people, mainly young children, develop serious complications and may have to go to hospital. When children have chickenpox they have to stay at home from creche and school, and their parents or other members of their family may have to take time off work to care for them. Most people only get chickenpox once, but those who do get it can also get shingles, usually when they are older.

A vaccine for chickenpox was developed in the 1970s. Australia, Canada, Germany, Italy, New Zealand and the USA are some of the countries that have a chickenpox vaccination programme for children. In Ireland, the chickenpox vaccine is not included in the vaccination programme for children that is provided by the Health Service Executive (HSE). However, a chickenpox vaccine is available to buy if parents or guardians want their child vaccinated.

The Health Information and Quality Authority (HIQA) was asked by the Department of Health to carry out a health technology assessment (HTA) of adding chickenpox vaccination to the current vaccination programme for children in Ireland. This assessment looked at the evidence of the effectiveness and safety of the chickenpox vaccine. The assessment also covered the value for money, cost, organisational, social and ethical issues of providing a chickenpox vaccination programme.

Three different chickenpox vaccination programmes were assessed:

- one-dose of the vaccine, given at 12 months of age
- two-doses of the vaccine, given at 12 months and 15 months of age
- two-dose of the vaccine, given at 12 months and five years of age

The chickenpox vaccine is effective in preventing chickenpox, including severe chickenpox and its complications. Two doses of the vaccine were found to be more effective than one dose. The chickenpox vaccine was also found to be safe. The main reactions are mild pain, redness and swelling of the skin. Fever and rash can occur often but serious harms are rare.

We assessed whether a chickenpox vaccination programme was good value for money. A one-dose chickenpox vaccination programme for children would be the best use of healthcare resources. A two-dose programme prevents more chickenpox

cases but it also costs more than a one-dose programme. If people have to take time off work because they have chickenpox or are minding someone with chickenpox and their loss of pay is included, then a chickenpox vaccination programme would be cost saving. The cost of providing a chickenpox vaccination programme for children was estimated at between €13 million for the one-dose programme and up to €28 million for the two-dose programme over a five year period.

Children currently receive their vaccines from either their GP or at school. One of the main challenges with providing a chickenpox vaccination programme would be ensuring that sufficient human resources are available within the primary care and schools-based settings to administer another vaccine. It would be important to provide an information campaign to parents about the benefits and harms of the chickenpox vaccine as they will be making the decision on giving their child the vaccine. An education programme on the chickenpox vaccine for healthcare workers involved in giving the vaccines to children would also be important.

The chickenpox vaccine will protect those who receive it. If enough children are vaccinated, then other people in the population who are not eligible to receive the vaccine may also be protected from chickenpox. Some people cannot get the vaccine because they have weak immune systems, for example.

Chickenpox is very common in Ireland and most people will not need to see a doctor when they have it. However, a small number of people, mostly young children, can get very sick and will need to go to hospital. Vaccination is very effective in preventing chickenpox and its complications, and it is safe. A chickenpox vaccination programme for children in Ireland would be a good use of resources.

# List of abbreviations used in this report

| | |
|---|---|
| **AMSTAR** | A MeaSurement Tool to Assess systematic Reviews |
| **BIA** | budget impact analysis |
| **BV** | breakthrough varicella |
| **CCA** | corrected covered area |
| **CDC** | Centers for Disease Control and Prevention |
| **CEA** | cost-effectiveness analysis |
| **CHO** | Community Healthcare Organisation |
| **CIDR** | computerised infectious disease reporting |
| **CPI** | consumer price index |
| **CSO** | Central Statistics Office |
| **CUA** | cost-utility analysis |
| **DRG** | diagnosis-related group |
| **DSA** | deterministic sensitivity analysis |
| **EAG** | expert advisory group |
| **EEA** | European Economic Area |
| **ECDC** | European Centre for Disease Prevention and Control |
| **EMA** | European Medicines Agency |
| **EU** | European Union |
| **EUnetHTA** | European Network of HTA |
| **EU-SILC** | European Union – Statistics on Income and Living Conditions |
| **GAS** | Group A streptococcus |
| **GP** | general practitioner |
| **GRADE** | Grading of Recommendations, Assessment, Development and Evaluations |
| **HIPE** | Hospital In-Patient Enquiry |
| **HIQA** | Health Information and Quality Authority |
| **HPO** | Healthcare Pricing Office |
| **HPRA** | Health Products Regulatory Authority |
| **HPSC** | Health Protection Surveillance Centre |
| **HSE** | Health Service Executive |
| **HTA** | health technology assessment |
| **HZ** | herpes zoster |
| **ICER** | incremental cost-effectiveness ratio |
| **ICU** | intensive care unit |

| | |
|---|---|
| **LOS** | length of stay |
| **MMR** | measles mumps rubella |
| **MMRV** | measles mumps rubella varicella |
| **NIAC** | National Immunisation Advisory Committee |
| **NIO** | National Immunisation Office |
| **OTC** | over the counter |
| **PCRS** | Primary Care Reimbursement Service |
| **PPP** | purchasing power parity |
| **PRIOR** | Preferred Reporting Items for Overviews of Reviews |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-analyses |
| **PSA** | probabilistic sensitivity analysis |
| **QALY** | quality-adjusted life year |
| **RCT** | randomised controlled trial |
| **RR** | relative risk |
| **SIP** | Schools Immunisation Programme |
| **SORT** | Strength of Recommendation Taxonomy |
| **SR** | systematic review |
| **UVV** | universal varicella vaccination |
| **VAT** | value added tax |
| **VE** | vaccine effectiveness |
| **VZV** | varicella zoster virus |
| **WHO** | World Health Organization |
| **WTP** | willingness to pay |

# 1 Introduction

## 1.1 Background to the request

Varicella-zoster virus (VZV) is a member of the herpesvirus group and is associated with two distinct clinical syndromes, varicella, commonly known as chickenpox, and herpes zoster, commonly known as shingles. Primary infection results in varicella, after which the virus remains in the body as a latent infection. The virus may reactivate after a period, typically several decades later, resulting in herpes zoster.

Varicella is a common, acute infectious disease, mainly affecting children. The annual incidence of varicella in EU/EEA countries typically approximates the annual birth cohort;[(1)] the total number of births in Ireland in 2020 was approximately 56,000.[(2)] In 2018, 81% of varicella notifications from sentinel general practice (GP) sites in Ireland related to children aged less than nine years of age.[(3)] Approximately 96% of those who are exposed to the VZV and who are not immune due to a history of varicella, will develop the disease.[(4)] Varicella is typically mild, and although complications are uncommon in otherwise healthy children, they may include superinfection (usually with Group A streptococcus), skin scarring, and rarely encephalitis, pneumonia, glomerulonephritis, myocarditis, hepatitis and coagulopathy.[(3)] The most frequent complications are skin and soft tissue superinfections, followed by neurological and pulmonary complications.[(1)]

The World Health Organization (WHO) advises that the introduction of routine childhood varicella vaccination should be considered in countries where varicella is an important public health burden and resources are sufficient to ensure sustained vaccination coverage of at least 80%.[(5)] Similarly, the European Centre for Disease Prevention and Control (ECDC) recommends that in considering the introduction of a varicella immunisation programme, individual countries should assess both their epidemiological and socioeconomic situations and their capacity to achieve high vaccination coverage.[(1)] In 2018, 36 countries and regions globally had introduced universal varicella vaccination, though not all programmes were publicly funded.[(6)] However, these established varicella vaccination programmes are heterogeneous, with a number of important differences between them as follows:

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

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

Following a formal request from the Department of Health, with support from the National Immunisation Advisory Committee (NIAC), the Health Information and Quality Authority (HIQA) has agreed to undertake a health technology assessment (HTA) in relation to universal varicella vaccination for children in Ireland. The aim of the HTA is to establish the clinical and economic impact of an expansion of the childhood immunisation schedule to include varicella vaccination.

## 1.2 Terms of reference

The HTA will be submitted as advice to the Department of Health to inform a decision as to whether and how an expansion of the childhood immunisation schedule to include varicella vaccination, should be implemented. 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, are to:

- describe the vaccines approved and vaccination options for immunisation against varicella
- describe the epidemiology and burden of disease associated with childhood varicella in Ireland
- review the current evidence of the clinical effectiveness and safety of potential varicella vaccination strategies for children
- review the current evidence of the cost-effectiveness of varicella vaccination programmes for children
- assess the cost-effectiveness and budget impact of expanding the childhood immunisation schedule to include varicella vaccination
- consider any potential organisational and resource implications of expanding the childhood immunisation schedule to include varicella vaccination
- consider any ethical and social implications that an expansion of the childhood immunisation schedule to include varicella vaccination may have for patients, parents, the general public or the healthcare system in Ireland
- based on the evidence in this assessment, provide advice to the decision maker on the expansion of the childhood immunisation schedule in Ireland to include varicella vaccination.

## 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 the Department of Health, the Health Service Executive – the National Immunisation Office, Primary Care and Public Health Medicine, the National Immunisation Advisory Committee (NIAC), the Health Protection Surveillance Centre (HPSC), the Irish College of General Practitioners, clinicians with specialist expertise in infectious diseases, Cuidiú - a parent advocacy group, and a methodological expert. The role of the EAG is 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 are to:

- contribute to the provision of high quality and considered advice by the Authority to the Department of Health
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to the Authority regarding the scope of the analysis
- support the Evaluation Team led by the Authority 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 the Authority's development of its approach to HTA by participating in an evaluation of the process upon the conclusion of the assessment.

The terms of reference of the HTA will be reviewed by the EAG at its first meeting. Draft chapters on the description of the technology, epidemiology and burden of disease, and overview of reviews of clinical effectiveness and safety were circulated to the EAG and will also be discussed at that meeting. Considerations regarding the other domains of the HTA will be discussed at the second/third meeting of the group. Draft versions of the completed report will be circulated for review by the EAG and amended as appropriate before a final draft report is prepared for public consultation. After the public consultation, a final draft version of the report will be circulated for review by the EAG. The report will be submitted to the Board of HIQA for approval. Following its approval, the completed assessment will be 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

- Varicella is a common, highly infectious, but vaccine-preventable, disease caused by the varicella zoster virus. Approximately 96% of those who are exposed to the VZV and are not immune, through prior infection or vaccination, will develop the disease.
- Varicella mainly affects children and the annual incidence in EU/EEA countries typically approximates the annual birth cohort; the total number of births in Ireland in 2021 was approximately 58,500.
- Four vaccines are licensed and marketed in Europe to prevent primary VZV infection, of which one is currently marketed for use in Ireland; the monovalent vaccines Varivax® (marketed in Ireland) and Varilrix® and the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines, ProQuad® and Priorix-Tetra®. The vaccines differ in terms of recommended dosing intervals, interchangeability and co-administration with other vaccines.
- The USA was the first country to license the monovalent vaccine for universal routine vaccination of persons aged at least 12 months in 1995, while Germany was the first country in Europe to recommend nationwide universal childhood varicella vaccination in 2004. Approval for the quadrivalent MMRV vaccine was granted in 2005 in the USA and in 2006 in Europe.
- Since the mid-1990s, the number of countries that have introduced funded universal childhood varicella vaccination programmes has grown and currently includes nine EU/EEA countries as well as Australia, Canada and New Zealand among others.
- Established varicella vaccination programmes are heterogeneous and differ according to the recommended dosing schedule, type of vaccine(s) recommended, age at which the first dose is recommended and the interval between doses where a two-dose schedule is in place.

## 2.1 Introduction

The purpose of this chapter is to describe the four varicella vaccines licensed in Europe that serve as the primary prevention tool to prevent varicella zoster virus (VZV) infection causing varicella and its sequelae. 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 childhood varicella immunisation programmes currently in place in Europe and a select number of other countries is provided. Lastly, the current childhood immunisation schedule in Ireland is described.

## 2.2 Pathogen

Varicella zoster virus is a double-stranded deoxyribonucleic acid (DNA) virus and one of eight herpesviruses known to routinely infect humans only.[7] 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.[7] VZV is one of three alpha herpesviruses (including herpes simplex virus 1 and 2);[7] they are human neurotropic viruses, that is, they can infect nerve cells and cause neurological manifestations.[8]

VZV is usually transmitted by inhalation of respiratory droplets, by direct contact with vesicular fluid, or by contact with fomites.[3] It enters the host through the respiratory tract or conjunctiva, replicating at the point of entry in the nasopharynx and in regional lymph nodes.[9]

## 2.3 Disease

Varicella is a common, highly infectious disease mainly affecting children. Approximately 96% of those who are exposed to the VZV and who are not immune by previously having varicella will develop the disease.[4] The incubation period is 10 to 21 days, with the majority developing the disease within 14 to 16 days.[3] Varicella is characterised by a pruritic rash that develops on the torso, face and limbs over a number of days and progresses rapidly from macules to papules to vesicular lesions before crusting as they dry. The disease is considered contagious starting one to two days before rash onset until all the lesions have crusted. Varicella is typically a mild, self-limiting illness. However, varicella can lead to serious complications and death in healthy and immunocompromised individuals.[10, 11] Serious complications include bacterial superinfection (usually with Group A streptococcus) of skin lesions with or without sepsis, central nervous system involvement (cerebellar ataxia, encephalitis and stroke), pneumonia, and other rare complications such as glomerulonephritis, myocarditis, hepatitis and coagulopathy.[3]

## 2.4 Detection of varicella zoster virus and immune response after infection

Varicella diagnosis is primarily clinical, although diagnosis can also be confirmed by laboratory testing using a swab of vesicular fluid, if necessary.[3] Serology is also available and can be used to demonstrate immunity. For most people, recovery from varicella usually results in lifelong immunity.[3, 9] While recurrent disease is rare, it is possible, but is more likely in immunocompromised individuals.[3]

## 2.5 Vaccines

### 2.5.1 Vaccine description

A live attenuated varicella vaccine was first developed in Japan in the 1970s and varicella vaccines first became commercially available in the 1980s. Currently there are four varicella vaccines authorised for vaccination against varicella by either the Health Products Regulatory Authority (HPRA) in Ireland or the European Medicines Agency (EMA). All four are live attenuated vaccines, two monovalent (varicella only) and two quadrivalent (combined measles, mumps, rubella and varicella [MMRV]) vaccines.

Of the four vaccines, Varivax® (Merck Sharp Dohme [MSD]), a monovalent vaccine authorised since 2003, is the only varicella vaccine that is currently marketed in Ireland.[12] Varilrix® (GlaxoSmithKline [GSK]), another monovalent vaccine, has been authorised in the EU via national procedures since 1994 and by 2021 was licensed in a total 21 EU countries as well as Iceland, Norway and the UK.[13] However, authorisation via national procedures led to inconsistencies in the way the medicine could be used across Member States. Following an EMA review of Varilrix®, published in February 2021, that recommended changes to the prescribing information in order to harmonise the way the medicine is used in the EU, an authorisation update for Varilrix® was issued in April 2021.[13] The Varilrix® licence planned for registration in Ireland will be harmonised with the other EU member states through the EU Mutual Recognition Procedure.[14] The EMA granted authorisation for ProQuad® (Sanofi Pasteur MSD) in April 2006[15] and the HPRA granted authorisation for Priorix-Tetra® (GSK) in August 2007,[16] both of which are quadrivalent MMRV vaccines.

Both monovalent vaccines and one quadrivalent vaccine (ProQuad®) are indicated for children from 12 months of age,[17-19] while the second quadrivalent vaccine (Priorix-Tetra®) is indicated for children from 11 months of age.[20] However, all four vaccines can be administered from nine months of age under special circumstances, such as to conform with national vaccination schedules or in outbreak situations. A

review of international varicella vaccination programmes suggests that varicella vaccination is not currently being routinely administered to children less than 11 months of age.

### 2.5.2 Co-administration with other vaccines

Based on the summary of product characteristics provided by the vaccine manufacturers, the following points are noted with regard to co-administration of the four licensed varicella vaccines with other vaccines:

- Concurrent administration of Varivax® with tetravalent, pentavalent or hexavalent (diphtheria, tetanus, and acellular pertussis [DTaP])-based vaccines has not been evaluated.[19]
- Separate vaccinations could be considered, when possible, for Priorix-Tetra® and Bexsero® (Meningococcal serogroup B [MenB] vaccine), due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when co-administered.[20]
- Meningococcal serogroup B (MenB) vaccine is not listed as one of the vaccines that may be co-administered with Varivax® and ProQuad®.[18, 19]

A summary of the key characteristics of each of the four varicella vaccines licensed in Europe is provided in Table 2.1.

## Table 2.1 Summary of key characteristics of the licensed varicella vaccines available in Ireland

| Vaccine | Monovalent | | Quadrivalent | |
|---|---|---|---|---|
| **Trade Name** | Varivax®[19] | Varilrix®[14, 17] | ProQuad®[18] | Priorix-Tetra®[20] |
| **Manufacturer** | Merck Sharp & Dohme (MSD) | GlaxoSmithKline (GSK) Biologicals | Sanofi Pasteur MSD | GlaxoSmithKline (GSK) Biologicals |
| **License Issued** | 04/11/2003 | Not licensed in Ireland (licensed in 21 EU countries plus Iceland, Norway and UK).<br>Authorised in EU countries via national procedures since 1994. EU authorisation update issued on 21 April 2021 following a request from GSK to EMA to harmonise the marketing authorisations for Varilrix® in the EU.<br>Licence registration in Ireland will be via the EU Mutual Recognition Procedure, thereby harmonising the licence with the other EU member states. | 06/04/2006 | 10/08/2007 |
| **Formulation** | 1 dose (0.5 mL) contains:<br>Varicella virus (produced in MRC-5 human diploid cells) Oka/Merck strain (live, attenuated) ≥1350 PFUs. | 1 dose (0.5 mL) contains:<br>Varicella virus[1] Oka strain (live, attenuated) not less than $10^{3.3}$ PFU<br>[1] Produced in human diploid cells (MRC-5) | 1 dose (0.5 mL) contains:<br>▪ Measles virus[1] Enders' Edmonston strain (live, attenuated) not less than 3.00 $\log_{10}$ $TCID_{50}$<br>▪ Mumps virus[1] Jeryl Lynn™ (Level B) strain (live, attenuated) not less than 4.30 $\log_{10}$ $TCID_{50}$<br>▪ Rubella virus[2] Wistar RA 27/3 strain (live, attenuated) not less than 3.00 $\log_{10}$ $TCID_{50}$<br>▪ Varicella virus[3] Oka/Merck strain (live, attenuated) not less than 3.99 $\log_{10}$ PFUs<br>[1] Produced in chick embryo cells<br>[2] Produced in human diploid lung (WI-38) fibroblasts<br>[3] Produced in human diploid (MRC-5) cells | 1 dose (0.5 ml) contains:<br>▪ Measles virus[1] Schwarz strain (live, attenuated) not less than $10^{3.0}$ $CCID_{50}$<br>▪ Mumps virus[1] RIT 4385 strain, derived from Jeryl Lynn strain (live, attenuated) not less than $10^{4.4}$ $CCID_{50}$<br>▪ Rubella virus[2] Wistar RA 27/3 strain (live, attenuated) not less than $10^{3.0}$ $CCID_{50}$<br>▪ Varicella virus[2] Oka strain (live, attenuated) not less than $10^{3.3}$ PFUs<br>[1] Produced in chick embryo cells<br>[2] Produced in human diploid (MRC-5) cells |
| **Population** | Individuals from 12 months of age.<br><br>Can be administered to infants from 9 months of age under special circumstances, such as to conform with national vaccination schedules or in outbreak situations. | Individuals from 12 months of age.<br><br>Under special circumstances, it can also be used to vaccinate infants from 9 months of age. | Individuals from 12 months of age.<br><br>May also be given to children from 9 months of age in certain situations, for example as part of a national vaccination programme, during an outbreak or for travel to a region where measles is common. | Individuals from the age of 11 months.<br><br>Use in infants aged 9-10 months could be considered under special circumstances, for example, if an epidemiological situation requires it. |

| Vaccine | Monovalent | | Quadrivalent | |
|---|---|---|---|---|
| **Trade Name** | Varivax®[19] | Varilrix®[14, 17] | ProQuad®[18] | Priorix-Tetra®[20] |
| **Therapeutic Indications** | Active immunisation against varicella.<br><br>Varivax® can be administered at the same time as, but at a different injection site from, a combined measles, mumps, and rubella vaccine, haemophilus influenzae type b conjugate vaccine, hepatitis B vaccine, diphtheria/tetanus/whole-cell pertussis vaccine, and oral polio virus vaccine. There was no evidence of a clinically relevant difference in the immune responses to any of the antigens when co-administered with Varivax.<br><br>If varicella vaccine is not given concomitantly with measles, mumps, and rubella virus vaccine live, a one-month interval between the two live virus vaccines should be observed.<br><br>Concurrent administration of Varivax® and tetravalent, pentavalent or hexavalent (diphtheria, tetanus, and acellular pertussis [DTaP])-based vaccines has not been evaluated. | Active immunisation against varicella.<br><br>Healthy individuals<br>Concomitant administration of Varilrix (at separate injection sites) with any of the following monovalent or combination vaccines is supported: measles-mumps-rubella (MMR), diphtheria-tetanus-acellular pertussis (DTaP), reduced antigen diphtheria-tetanus-acellular pertussis (DTaP), Haemophilus influenzae type b (Hib), inactivated polio (IPV), hepatitis B (HBV), hexavalent vaccine (DTPa-HBV-IPV/Hib), hepatitis A vaccine (HAV), meningococcal serogroup B vaccine (Bexsero), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W and Y conjugate vaccine (MenACWY) and pneumococcal conjugate vaccine (PCV).<br><br>If a measles vaccine is not given at the same time as Varilrix, there should be an interval of at least one month between the administration of these vaccines. | Active immunisation against measles, mumps, rubella, and varicella.<br><br>ProQuad® can be given simultaneously (but at separate injection sites) with Prevenar and/or hepatitis A vaccine, or with monovalent or combination vaccines comprised of diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, or hepatitis B antigen. | Active immunisation against measles, mumps, rubella, and varicella.<br><br>Priorix-Tetra can be given simultaneously (but at different injection sites) with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTaP-HBV-IPV/Hib)]: diphtheria-tetanus-acellular pertussis vaccine (DTaP), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), meningococcal serogroup B vaccine (MenB), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (MenACWY) and 10-valent pneumococcal conjugate vaccine.<br><br>Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero was co-administered with Priorix-Tetra, separate vaccinations can be considered when possible.<br><br>There are currently insufficient data to support the use of Priorix-Tetra with any other vaccines. |

**Key:** $CCID_{50}$ – cell culture infectious dose 50%; EMA - European Medicines Agency; EU - European Union; MRC-5 - Medical Research Council cell strain 5; PFU - plaque-forming units; $TCID_{50}$ – median tissue culture infectious dose; VZV - varicella zoster virus;

### 2.5.3 Administration and manufacturers stipulated storage

All four varicella vaccines should be injected subcutaneously or intramuscularly in the deltoid region of the upper arm or in the anterolateral area of the thigh. In the case of Varivax® and Pro-Quad®, the preferred injection sites are the anterolateral area of the thigh in younger children and the deltoid area in older children, adolescents, and adults.[17-20] All four vaccines should preferably be administered subcutaneously in subjects with thrombocytopenia or any coagulation disorder.[17-20] Both Varivax® and ProQuad® should be refrigerated (2°C to 8°C) when being stored and transported, and used immediately (or within 30 minutes if stored between 20°C and 25°C) after reconstitution.[18, 19] Priorix-Tetra® should be refrigerated (2°C to 8°C) when being stored and transported, and used immediately (or within 24 hours if refrigerated between 2°C and 8°C) after reconstitution.[20] As Varilrix® is not yet registered in Ireland, there are no storage instructions currently approved for the vaccine in Ireland. Based on correspondence received from the manufacturer,[14] Varilrix® will be registered in Ireland through the EU Mutual Recognition Procedure which currently instructs that the vaccine should be refrigerated (2°C to 8°C) when being stored (in the original package) and transported. After reconstitution, it is recommended that Varilrix® should be used as soon as possible but it has been demonstrated that the reconstituted vaccine may be kept for up to 90 minutes at room temperature (25°C) and up to 8 hours in the refrigerator (2°C to 8°C).

### 2.5.4 Dosing schedule

A two-dose regimen is recommended by the manufacturers for all four vaccines, with the interval between doses varying by vaccine and dependent on the age at which the first dose is administered. The recommended minimum interval between doses ranges from one month (Varivax® and ProQuad®) to six weeks (Varilrix® and Priorix-Tetra®).[17-20] Where the vaccine is administered to a child less than the indicated age for vaccination, but who is at least nine months old, the recommended minimum interval between doses is three months for all four vaccines.

### 2.5.5 Interchangeability of vaccines

The interchangeability of varicella vaccines differs between vaccines. For the monovalent vaccine Varilrix®, a single (second) dose may be administered to individuals who have already received a single dose of another varicella-containing vaccine.[17] Also, a single first dose of Varilrix® may be administered followed by a single (second) dose of another varicella containing-vaccine.[17] For the quadrivalent vaccine Priorix-Tetra®, a single dose may be administered to individuals who have already received a single dose of another measles, mumps and rubella (MMR) vaccine and or a single dose of another varicella vaccine.[20] Additionally, a single

dose of Priorix-Tetra® may be administered followed by a single dose of another measles, mumps and rubella (MMR) vaccine and or a single dose of another varicella vaccine.[20] The quadrivalent vaccine ProQuad®, may be used as the second dose in individuals who have previously received measles, mumps, and rubella (MMR) vaccine and a monovalent varicella vaccine.[18] The interchangeability of the monovalent vaccine Varivax® is not described in the product characteristics.[19] Table 2.2 provides a summary of the recommended dosing schedule, age at vaccination, intervals between doses and interchangeability for each vaccine.

## Table 2.2 Dosing schedules, age at vaccination and interchangeability for licensed varicella vaccines

| Vaccine | Vaccine type | Age at vaccination* | Recommended dosing schedule (per Summary of Product Characteristics ) | Interchangeability of varicella vaccines |
|---|---|---|---|---|
| Varivax® (MSD)[19] | Monovalent (varicella) | 9-12mths | 2 doses ≥3 months apart‡ | Not specified in Product Summary Characteristics. |
| | | 12mths-12yrs | 2 doses ≥1 month apart‡ | |
| | | ≥13yrs | 2 doses 4-8 weeks apart‡ | |
| Varilrix® (GSK)[17] | Monovalent (varicella) | 9-11mths | 2 doses ≥3 months apart‡ | ▪ A single dose of Varilrix may be administered to those who have already received a single dose of another varicella-containing vaccine.<br>▪ A single dose of Varilrix may be administered followed by a single dose of another varicella containing vaccine. |
| | | ≥12mths | 2 doses ≥6 weeks apart‡ | |
| ProQuad® (Sanofi Pasteur MSD)[18] | Quadrivalent (MMRV) | 9-12mths | 2 doses ≥3 months apart‡ | ▪ ProQuad may be used as the second dose in individuals who have previously received measles, mumps, and rubella (MMR) vaccine and a varicella vaccine. |
| | | ≥12mths | 1 dose followed 1-3 months later by:‡<br>2nd dose MMRV<br>OR<br>1 dose monovalent | |
| Priorix-Tetra® (GSK)[20] | Quadrivalent (MMRV) | 9-10mths | 2 doses 3 months apart | ▪ A single dose of Priorix-Tetra may be administered to individuals who have already received a single dose of another measles, mumps and rubella (MMR) vaccine and/or a single dose of another varicella vaccine.<br>▪ A single dose of Priorix-Tetra may be administered followed by a single dose of another measles, mumps and rubella (MMR) vaccine and/or a single dose of another varicella vaccine. |
| | | ≥11mths | 1 dose followed 6 weeks (and not less than 4 weeks) to 3 months later by:<br>2nd dose MMRV<br>OR<br>1 dose monovalent | |

**Key:** GSK - GlaxoSmithKline; MMRV - measles, mumps, rubella, varicella; MSD - Merck Sharp & Dohme.
* Vaccination indicated in individuals aged at least 12 months of age, but can be administered from nine months under special circumstances (e.g., to conform with national vaccination schedules) ‡Two doses to receive optimal protection from varicella

## 2.6 Varicella vaccination

### 2.6.1 Varicella vaccination in Ireland

Varicella vaccination is currently not included in the routine childhood immunisation schedule in Ireland. However, the vaccine is available and can be paid for privately. Varicella vaccination is recommended for non-immune individuals without a definite history of varicella, proof of immunity or previous vaccination (from 12 months of age) in specific risk groups.[3] Clinical practice guidelines recommend varicella vaccination in women who are not immune and are planning a pregnancy or receiving infertility treatment.[21]

### 2.6.2 International varicella vaccination programmes for children

Varicella vaccination for children is currently universally recommended and funded by the national health system in nine EU/EEA countries (Finland,[22] Germany,[23] Greece,[24] Hungary,[25] Iceland,[26] Italy,[27] Latvia,[28] Luxembourg[29] and Spain[30]). It is also universally recommended in Austria and Cyprus, but is not funded by their national health systems.[25] Outside Europe, varicella vaccination is also included in the immunisation schedules in Australia,[31] Canada,[32] New Zealand[33] and the USA.[34] However, the varicella vaccination programmes in these countries are heterogeneous and there are a number of important differences (Table 2.3) between them including the dosing schedule, the type of varicella vaccine(s) recommended, the age at which the first varicella vaccine dose is recommended and the interval between doses where a two-dose schedule is in place. Of these countries, currently only Australia[31] and New Zealand[33] recommend a one-dose schedule. All European countries with universal childhood, government funded, varicella vaccination programmes currently recommend a two-dose schedule, with vaccination for varicella mandatory for school attendance in Hungary,[25] Italy[27] and Latvia.[28] A one-dose schedule was originally recommended in Germany,[23] Latvia[28] and the USA,[34] but these countries have since changed to a two-dose schedule. Similarly, a two-dose schedule is recommended in Canada.[32]

With respect to the type of vaccine administered, that is monovalent varicella or quadrivalent MMRV, within Europe a monovalent vaccine is exclusively recommended for both doses in Hungary,[25] Iceland[26] and Latvia,[28] while a quadrivalent MMRV vaccine is exclusively recommended for both doses in Luxembourg.[29] In Finland,[22] Germany[23] and Spain,[30] a monovalent varicella vaccine is recommended for the first dose and either a monovalent or the quadrivalent MMRV vaccine is recommended for the second dose. In Italy,[27] a monovalent or quadrivalent vaccine is recommended for both first and second doses. Outside Europe, Australia recommends one-dose monovalent vaccination[31] while

New Zealand recommends one-dose quadrivalent MMRV vaccination.[33] In both Canada[32] and the USA,[34] a monovalent or quadrivalent MMRV vaccine can be administered for both first and second doses.

The age at which the first vaccine dose is recommended by these countries is generally from 12 to 15 months, but this varies from 11 to 14 months in Germany[23] to administration at 18 months in Finland[22] and Australia.[31] Greater variation is evident in the age at which the second dose (where applicable) is recommended. It ranges from 15 to 23 months in Germany[23] to seven years old in Latvia.[28] The interval between first and second dose, based on recommended ages for each dose, ranges from three months in Hungary[25] to six years in Latvia.[28]

A number of the countries reviewed highlight the need for catch-up vaccination in non-vaccinated adolescents who do not have a history of varicella. Ages at which catch-up vaccination is indicated differ, ranging from nine to 17 years. Countries also differ in the use of one-dose and two-dose schedules for catch-up. As with its routine childhood immunisation programme, New Zealand recommends use of one-dose of monovalent vaccine for catch-up; Australia uses a one-dose schedule for its childhood programme, but recommends a two-dose schedule for catch-up. Finland, Germany and Canada use two-dose schedules for both their routine and catch-up programmes (Table 2.3).

## Table 2.3 International childhood varicella vaccination programmes

| European Countries | Year Introduced | Dosage | Age | Monovalent / Quadrivalent | Additional Information |
|---|---|---|---|---|---|
| Finland[22] | 2017 | Two-dose | Min. 18mths - 1st dose<br>6yrs - 2nd dose | Mono 1st dose<br>Mono/Quad 2nd dose dependent on age (Quad only for 6yr olds) | Programme is for all children born on or after 1 Jan 2006 who have not had chickenpox. Children who received the first dose at age 6-11yrs are offered a booster at 12yrs. Children aged ≥13yrs receive two doses with an interval of 3mths between doses. |
| Germany[23] | 2004 (1-dose)<br>2009 (2-dose) | Two-dose | 11-14mths - 1st dose<br>15-23mths - 2nd dose | Mono 1st dose<br>Mono/Quad 2nd dose | In all non-vaccinated 9-17yr old adolescents with no history of varicella, catch-up vaccination should also take place with two doses. |
| Greece[24] | 2006 | Two-dose | 12-15mths - 1st dose<br>4-6yrs - 2nd dose | Unclear | Not applicable |
| Hungary[25] (mandatory) | 2018 | Two-dose | 13mths - 1st dose<br>16mths - 2nd dose | Mono 1st dose<br>Mono 2nd dose | Not applicable |
| Iceland[26] | 2020 | Two-dose | 12mths - 1st dose<br>18mths - 2nd dose | Mono 1st dose<br>Mono 2nd dose | Not applicable |
| Italy[27] (mandatory) | 2017 | Two-dose | 13-15mths - 1st dose<br>5-6yrs - 2nd dose | Mono/Quad 1st dose<br>Mono/Quad 2nd dose | Not applicable |
| Latvia[28] (mandatory) | 2008 (1-dose)<br>2019 (2-dose) | Two-dose | 12-15mths - 1st dose<br>7yrs - 2nd dose | Mono 1st dose<br>Mono 2nd dose | Not applicable |
| Luxembourg[29] | 2010 | Two-dose | 12mths - 1st dose<br>15-23mths - 2nd dose | Quad 1st dose<br>Quad 2nd dose | Not applicable |
| Spain[30] | 2016 | Two-dose | 15mths - 1st dose<br>3-4yrs - 2nd dose | Mono 1st dose<br>Mono/Quad 2nd dose | Not applicable |
| **Other Countries** | **Year Introduced** | **Dosage** | **Age** | **Monovalent / Quadrivalent** | **Additional Information** |
| Australia[31] | 2005 (mono)<br>2013 (quad) | One-dose | 18mths | Quad | Two doses of monovalent vaccine are recommended for all non-immune people aged ≥14 years. |
| Canada[32] | 2000-2007<br>(by province/ territory) | Two-dose | 12-15mths - 1st dose<br>≥18mths (but no later than school entry) - 2nd dose | Mono/Quad 1st dose<br>Mono/Quad 2nd dose | Children aged 12 months to <13 years not immunised on the routine schedule should receive 2 doses of any varicella-containing vaccine. |
| New Zealand[33] | 2017 | One-dose | 15mths | Mono | Previously unvaccinated children turning 11 years old on or after 1 July 2017 who have not previously had a varicella infection should also receive 1-dose of monovalent vaccine. |
| USA[34]‡ | 1995 (1-dose)<br>2005 (2-dose) | Two-dose | 12-15mths - 1st dose<br>4-6yrs - 2nd dose | Mono/Quad 1st dose<br>Mono/Quad 2nd dose | People ≥13 years who have never had chickenpox or received chickenpox vaccine should get two doses, at least 28 days apart. |

‡For the 2018-2019 school year, 43 states and District of Columbia require children to receive two doses of chickenpox vaccine or have other evidence of immunity against chickenpox before starting school. There are eight states with a school-entry requirement of one dose of chickenpox vaccine or other evidence of immunity against chickenpox.
Additional Source for European countries: ECDC Vaccination Scheduler[25]

## 2.7 Current childhood immunisation schedule in Ireland

As of May 2022, the immunisation schedule for children in Ireland requires five visits for vaccination up to and including 13 months of age. The schedule includes additional vaccinations for school-aged children in junior infants (at four/five years of age) and at 12/13 years of age. A summary of the recommended childhood immunisation schedule in Ireland is provided in Table 2.4.

### Table 2.4 Recommended childhood immunisation schedule in Ireland 2020

| Age / School class | Vaccinations | Number of Vaccinations | Product Name[35] | Manufacturer[35] |
|---|---|---|---|---|
| 2 Months | 6 in 1 (DTaP/Hib/IPV/Hep B) | 3 injections + 1 oral | Infanrix Hexa | GSK |
| | + | | | |
| | PCV | | Prevenar 13 | Pfizer |
| | + | | | |
| | MenB | | Bexsero | GSK |
| | + | | | |
| | Rotavirus | | Rotarix | GSK |
| 4 Months | 6 in 1 (DTaP/Hib/IPV/Hep B) | 2 injections + 1 oral | Infanrix Hexa | GSK |
| | + | | | |
| | MenB | | Bexsero | GSK |
| | + | | | |
| | Rotavirus | | Rotarix | GSK |
| 6 Months | 6 in 1 (DTaP/Hib/IPV/Hep B) | 3 injections | Infanrix Hexa | GSK |
| | + | | | |
| | PCV | | Prevenar 13 | Pfizer |
| | + | | | |
| | MenC | | Menjugate | Novartis GSK |
| 12 Months | MMR | 2 injections | MMRVaxpro | MSD Ireland (Human Health) |
| | + | | | |
| | MenB | | Bexsero | GSK |
| 13 Months | Hib/MenC | 2 injections | Menitorix | GSK |
| | + | | | |
| | PCV | | Prevenar 13 | Pfizer |
| Junior Infants (4/5 Years) | 4 in 1 (DTaP/IPV*) | 2 injections | Tetravac | Sanofi Pasteur |
| | + | | | |
| | MMR | | MMRVaxpro | MSD Ireland (Human Health) |
| 12-13 Years | HPV (2 doses 6mths apart) | 4 injections | NR | NR |
| | + | | | |
| | Tdap | | NR | NR |
| | + | | | |
| | MenACWY | | NR | NR |

Source: Health Service Executive. Immunisation Guidelines. Chapter 2 General Immunisation Procedures. Dublin: HSE National immunisation Office; 2021.
*dTap/IPV can be given if DTaP/IPV is not available
**Key:** DTaP - diphtheria, tetanus and acellular pertussis; HepB - hepatitis B; Hib - haemophilius influenzae b; HPV - human papilloma virus; IPV - inactivated polio virus; GSK - GlaxoSmmithKline; MenACWY - meningococcal ACWY; MenB - meningococcal B; MenC - meningococcal C; MMR - measles, mumps and rubella; MSD - Merck Sharp & Dohme; NR - not reported; PCV - pneumococcal conjugate vaccine; Tdap - tetanus, low-dose diphtheria and low-dose acellular pertussis;

## 2.8 Discussion

Varicella is a common, highly infectious, vaccine-preventable, disease mainly affecting children. Although varicella is a mild self-limiting febrile illness, severe complications can occur. Approximately 96% of those who are exposed to the VZV and are not immune, through prior infection or vaccination, will develop the disease.[4] The annual incidence of varicella in EU/EEA countries typically approximates the annual birth cohort;[1] the total number of births in Ireland in 2020 was approximately 56,000.[2]

Four vaccines are licensed and marketed in Europe to prevent primary VZV infection, of which one is currently marketed for use in Ireland: the monovalent vaccines Varivax® (marketed in Ireland), produced by MSD, and Varilrix®, produced by GSK, and the quadrivalent MMRV vaccines, ProQuad®, produced by MSD and Priorix-Tetra®, produced by GSK. The vaccines differ in terms of recommended dosing intervals, interchangeability and co-administration with other vaccines.

Following the first licensing of the monovalent varicella vaccine in the 1980s, the USA became the first country to license the monovalent vaccine for universal routine vaccination of persons aged at least 12 months in 1995.[36] Germany was the first country in Europe to recommend nationwide universal childhood varicella vaccination in 2004.[37] Approval for the quadrivalent MMRV vaccine followed in 2005 in the USA[38] and in 2006 in Europe.[39] Over this time, the number of countries that have introduced funded universal childhood varicella vaccination programmes has continued to grow, and now includes nine EU/EEA countries as well as Australia, Canada and New Zealand among others. However the vaccination programmes in these countries are heterogeneous and differ according to the recommended dosing schedule, type of varicella vaccine(s), age at which the first dose is recommended and the interval between doses where a two-dose schedule is in place.

# 3 Epidemiology and Burden of Disease

## Key points

- Varicella is a common, acute and highly contagious disease, caused by the VZV virus, mainly affecting children. Estimates of the basic reproduction number indicate a range of 10-12, meaning that one case of varicella potentially infects 10-12 susceptible others. After VZV infection, most people develop immunity for the remainder of their lives.
- The annual incidence rate of VZV primary infection (derived from seroprevalence data) in Ireland has been estimated at:
    - 11,954 per 100,000 population in those aged less than five years,
    - 6,434 per 100,000 population in those aged five to nine years, and
    - 76 per 100,000 population in those aged 10 to 14 years.
- Seroprevalence of antibodies against varicella in those aged less than 15 years in Ireland has been estimated at 92.3%, reaching 95.3% in those aged less than 65 years.
- While varicella is typically a mild disease, serious complications occur, including skin and soft tissue bacterial superinfection, central nervous system involvement and pneumonia, and other rare gastrointestinal, hepatic and haematological complications requiring hospitalisation.
- A total of 2,717 hospital admissions with a principal diagnosis of varicella (96.3% had no underlying condition) were reported over a 12 year period from 2005 to 2016, with an average of 226 admissions per annum, with infants and young children comprising the majority of admissions.
- Primary infection with VZV results in varicella, after which the virus becomes latent in the body's nervous system. The virus may reactivate after a period, sometimes several decades later, resulting in herpes zoster (shingles). The lifetime risk of developing herpes zoster is approximately 30%.
- Morbidity associated with herpes zoster increases with age and the most common complication is post-herpetic neuralgia; persistent pain (for more than 90 days after onset) in the area of the rash with the potential to cause significant reductions in quality of life, activity, mood and sleep.

- Although limited research has been published examining the total economic burden of varicella in Ireland, estimates suggest that the burden, including both direct and indirect costs, is likely to be considerable.

## 3.1 Introduction

This chapter describes the epidemiology of varicella in Ireland and the burden of disease associated with primary varicella zoster virus (VZV) infection. Although the proposed programme of varicella vaccination relates to children only, varicella is a highly communicable disease and incidence in adolescents and adults is also relevant. Additionally, given that herpes zoster is caused by reactivation of the VZV virus following primary infection, the epidemiology of herpes zoster is also briefly summarised.

Varicella is a common, acute and highly contagious disease mainly affecting children. The average incubation period for varicella is 14 to 16 days following exposure to an infectious individual with varicella or herpes zoster.[40] It may begin with cold-like symptoms, followed by a high temperature, and is characterised by a pruritic (itchy), blister-like rash, mostly on the face and torso, typically lasting four to seven days.[4]

A person with chickenpox is considered contagious before rash onset until all the chickenpox lesions have crusted.[40] Estimates of the basic reproduction number for varicella indicate a range of 10-12, meaning that one case of varicella potentially infects 10-12 susceptible others.[3] Secondary attack rates among susceptible household contacts range from 61% to 100%.[41] Approximately 96% of those who are exposed to the VZV and who are not immune due to previous infection or vaccination, will develop the disease.[4] After VZV infection, most people develop immunity for the remainder of their lives, with recurrent varicella very rare.[42]

## 3.2 Incidence of varicella in Ireland and natural history of VZV infection

### 3.2.1 Introduction

The annual incidence of varicella in EU/EEA countries typically approximates the annual birth cohort;[1] the total number of births in Ireland in 2021 was approximately 58,500.[2] Incidence in the community in Ireland is estimated from data obtained from the sentinel surveillance programme for varicella, one of several sentinel general practice surveillance programmes for clinical diseases in Ireland.[43] The sentinel programme comprises a network of 60 general practices (representing 5.7% of the population) that report, on a weekly basis, nationally representative data on the number of patients who consult for specific clinical diseases.[43]

### 3.2.2 Children

Based on data gathered from the sentinel practices from 2005 to 2019 inclusive, children aged less than 10 years represented 76% (2005) to 87% (2014) of all varicella notifications. Over the same time period, children aged less than five years represented 49% (2013) to 62% (2017) of all varicella notifications.[44] For 2019 (provisional data), the most recent year that data are available, 85% of all varicella notifications from sentinel general practices related to children less than 10 years of age and 59% of all notifications related to children less than 5 years of age.[44] The annual incidence rate of VZV primary infection (derived from seroprevalence data published between 1995 and 2016) in Ireland has been estimated at 11,954 per 100,000 population in those aged less than five years, 6,434 per 100,000 population in those aged five to nine years and falling to 76 per 100,000 population in those aged 10 to 14 years.[45] The estimated annual incidence rates of VZV primary infection for the population by age (up to 64 years old) are reported in Table 3.1.

**Table 3.1 Age-specific annual incidence (per 100,000) of varicella zoster virus primary infection in Ireland**

| Age group | Estimated Incidence of VZV per 100,000 population | |
|---|---|---|
| | Mean | (95% confidence interval) |
| < 5 years | 11,954 | (10,730 - 13,152) |
| 5 to 9 years | 6,434 | (4,946 - 7,768) |
| 10 to 14 years | 76 | (0 - 426) |
| 15 to 19 years | 72 | (0 - 338) |
| 20 to 39 years | 64 | (0 - 208) |
| 40 to 64 years | 52 | (0 - 90) |

Source: Bollaerts K et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: deriving incidence from seroprevalence data. Epidemiology & Infection. 2017;145(13):2666-77.
Key: VZV – varicella zoster virus;

### 3.2.3 Adults

While varicella is typically a childhood illness, it can and does affect adults. Varicella is often more severe in adults than children, with complications also more common. Based on data gathered from the sentinel practices from 2005 to 2019 inclusive, adults aged ≥20 years represented 5% (2014) to 14% (2005) of all varicella notifications.[44] For 2019 (provisional data), the most recent year that data are available, 8% of all varicella notifications from sentinel general practices related to adults ≥20 years.[44] The annual incidence rate of VZV primary infection (derived from seroprevalence data) in adults in Ireland has been estimated at 64 cases per 100,000 population in those aged 20-39 years and 52 cases per 100,000 population in those aged 40-64 years (Table 3.1).[45]

### 3.2.4 Pregnant women

Although a significant proportion of women will have had varicella as a child, varicella is estimated to cause complications in approximately three in every 1,000 pregnancies.[46] Varicella may cause severe disease in susceptible pregnant women (primarily pneumonia, as well as hepatitis and encephalitis), fetal death or congenital varicella syndrome, characterised by limb hypoplasia, cutaneous scarring, ocular and central nervous system abnormalities. Increased morbidity and mortality has been reported in pregnant women who develop varicella, with pneumonia occurring in approximately 10-20% of cases.[47-50] Risks to the fetus and neonate are related to the timing of maternal infection.[3, 51] If a pregnant woman develops varicella in her first or early second trimester, her baby has a small risk (0.4 to 2.0%) of being born with fetal varicella syndrome, potentially causing scarring on the skin, abnormalities in limbs, brain, and eyes, and low birth weight.[40, 51] If a woman develops VZV infection in the last four weeks of her pregnancy, there is a significant risk of varicella to the new-born (up to 50% of babies are infected and approximately 23% of these develop clinical varicella).[51] Severe varicella is most likely to occur if the infant is born within 15 days of onset of the mother's rash or if the mother develops the rash up to seven days after delivery.[51]

### 3.2.5 Seroprevalence

Based on a systematic review of seroprevalence studies that included data from 16 European countries, it was estimated that prior to the introduction of universal varicella vaccination, over 85% of the population has been infected by VZV by the age of 15 years.[45] Seroprevalence of antibodies against varicella in those aged less than 15 years in Ireland was estimated at 92.3%, reaching 95.3% in those aged less than 65 years (Table 3.2)

**Table 3.2 Age-specific seroprevalence (%) of antibodies against varicella in Ireland**

| Age group | Seroprevalence (%) of antibodies against varicella in Ireland | |
|---|---|---|
| | Mean | (95% confidence interval) |
| <5 years | 59.8 | (53.7 - 66.3) |
| <10 years | 91.9 | (88.8 - 93.5) |
| <15 years | 92.3 | (90.6 - 93.6) |
| <20 years | 92.7 | (91.6 - 93.7) |
| <40 years | 94.0 | (91.9 - 96.9) |
| <65 years | 95.3 | (91.9 - 98.9) |

Source: Bollaerts K et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: deriving incidence from seroprevalence data. Epidemiology & Infection. 2017;145(13):2666-77.

### 3.2.6 Outbreaks

Infectious disease regulations in Ireland specify that unusual clusters or changing patterns of illness that may be of public health concern must be reported. Thus, varicella outbreaks (regardless of hospitalisation status) must be notified. Two outbreaks of suspected varicella were notified in 2018. One outbreak occurred in a childcare facility where 20 people were ill and one occurred in a residential institution where three people were ill.[52]

## 3.3 Burden of disease

While varicella is typically a mild disease, serious complications include skin and soft tissue bacterial superinfections (usually Group A streptococcus), as well as central nervous system involvement (cerebellar ataxia, stroke and encephalitis), pneumonia and other rare gastrointestinal, hepatic and haematological complications requiring hospitalisation.[1] In addition to its association with bacterial superinfection of skin lesions, varicella is a neurotropic virus and it is recognised as among the most common causes of stroke in childhood. While varicella is potentially more severe in individuals with immunodeficiency, the majority of serious complications occur in otherwise healthy children.

### 3.3.1 General Practitioner attendance

Data on general practitioner (GP) attendance due to varicella in Ireland are not available, other than from the sentinel data. A UK study analysed general practice records from in excess of eight million people, over a 10 year period from 2005 to 2014, and reported data on the burden of varicella on UK general practice.[53] For each of the 10 year periods analysed, estimated consultation rates were highest among those aged one to three years, ranging from 61.2 consultations/1,000 person-years in 2007 to 39.7/1,000 person-years in 2014.[53] Overall, consultation rates fell with increasing age; the rates in those aged over 20 years were less than one varicella consultation/1,000 person-years throughout the study period.[53] A study estimating the overall burden of varicella in Europe before the introduction of universal varicella vaccination (UVV), estimated that 54% of all varicella cases in Europe lead to a physician consultation.[54] In the same study, annual primary care utilisation rates in Ireland were predicted to be 6,349 to 7,080/100,000 population in those aged less than five years and 2,768 to 3,878/100,000 population in those aged five to nine years.[54] It should be noted that these predictions were based on minimum-maximum observed primary care utilisation rates for varicella in other European countries and the authors did acknowledge that health care seeking behaviour, and therefore primary care utilisation rates, vary considerably between countries.[54]

### 3.3.2 Complications and Hospitalisation

In Ireland, the 1981 Infectious Disease Regulations and subsequent amendments identify a range of notifiable infectious diseases. Hospitalised cases of varicella became notifiable in 2011. In accordance with these regulations, medical practitioners, including clinical directors of diagnostic laboratories, are required to notify the Medical Officer of Health (MOH)/Director of Public Health (DPH) of cases of notifiable diseases. These data are reported to the Health Protection Surveillance Centre (HPSC) and are recorded in the Computerised Infectious Disease Reporting (CIDR) system.

In 2019, a total of 93 hospitalised varicella cases were notified to the HPSC.[55] However, due to the impact of the COVID-19 pandemic, the Annual Epidemiology Report from the HPSC for varicella (hospitalised cases) for 2019, with further detail on cases, will not be published. In 2018, the last full year before the COVID-19 pandemic for which data are available, a total of 99 hospitalised varicella cases were notified to the HPSC, representing a crude incidence rate of 2.1 notified hospitalised cases per 100,000 population. The highest age specific incidence rate of notifiable hospitalisations was in those aged less than one year and estimated at 30.5 notified cases per 100,000 population.[52] The number of notified cases from 2012 to week 18 of 2022 are provided in Table 3.3. The lower numbers of notified hospitalised cases in 2020 and 2021 likely reflect the impact of the COVID-19 pandemic on VZV circulation and resulting varicella disease.

## Table 3.3 Notified hospitalised cases of varicella in Ireland 2012-2022

| Year | Number of notified hospitalised cases | Crude incidence rate of notified hospitalised cases per 100,000 population | Age group with largest number of notified hospitalised cases | Age group with highest age specific incidence of notified hospitalised cases | Age specific incidence in age group with the highest age specific incidence of notified hospitalised cases‡ |
|---|---|---|---|---|---|
| 2022 - to week 18 (provisional) | 16 ᵞ(56) | NR | NR | NR | NR |
| 2021 (provisional) | 24 | NR | NR | NR | NR |
| 2020 | 26 | NR | NR | NR | NR |
| 2019 | 93 | NR | NR | NR | NR |
| 2018 | 99 | 2.1 | Not reported | <1 year | 30.5 |
| 2017 | 105 | 2.2 | Not reported | <1 year | 26.0 |
| 2016 | 106 | 2.2 | Not reported | <1 year | 19.0 |
| 2015 | 69 | 1.5 | Not reported | <1 year | 12.5 |
| 2014 | 61 | 1.3 | <1 year | <1 year | 21.0 |
| 2013 | 53 | 1.2 | 3-4 years | <1 year | 12.5 |
| 2012 | 80 | 1.7 | 1-2 years | 1-2 years | 16.0 |

Source: Health Protection Surveillance Centre, Health Service Executive. Infectious Disease Notifications in Ireland, 2019 - 2021 Dublin. HPSC & HSE; 2021. [Available from: https://www.hpsc.ie/notifiablediseases/annualidstatistics/Annual_ID_Summary_Report_for_HPSC_Web_2019-2021.pdf and Health Protection Surveillance Centre. Chickenpox-hospitalised cases in Ireland Annual Reports Dublin. HPSC; 2021. [Available from: https://www.hpsc.ie/a-z/vaccinepreventable/varicellachickenpox/surveillancereports/annualreports/
‡ Estimated from graphs in Annual Reports. Available at: https://www.hpsc.ie/a-z/vaccinepreventable/varicellachickenpox/surveillancereports/annualreports/
ᵞ Source: Health Protection Surveillance Centre Weekly Infectious Disease Report. Most recent weekly report is available at: https://www.hpsc.ie/notifiablediseases/weeklyidreports/ Historic weekly reports are not retained on the website.

Data from the Hospital Inpatient Enquiry System (HIPE) in Ireland have also been used to examine hospital admissions for patients with primary varicella infection.(57) A total of 2,717 admissions (96.3% had no underlying condition) were reported over a 12 year period (2005 to 2016), with an average of 226 admissions per annum. The annual incidence rate of varicella-related hospital admissions was estimated at 4.87 per 100,000 population.(57) Infants and young children comprised the majority of admissions; 47% were less than three years old and 76% were less than 10 years old.(57) For those aged less than 18 years, the highest number of admissions was in those aged one to two years for all years except 2010, where the number of admissions was highest in those aged less than one year.(57) A total of 757 (28%) admissions had a complicating diagnosis, the most common being cellulitis, volume depletion and streptococcal infection.(57) The average length of stay for varicella-related admissions was five days, although average length of stay for patients requiring intensive care treatment (n=62) was 26 days. The study estimated that chickenpox accounted for an average of 1,130 acute hospital and 161 ICU bed days annually over the study period.(57)

The difference between notified and HIPE cases of varicella-related hospitalisations is most likely related to case ascertainment. The majority of notified cases are those with laboratory confirmed varicella, whereas HIPE cases also include cases where

the diagnosis of varicella was a clinical one and laboratory confirmation was deemed unnecessary by the clinician. The estimated incidence of 4.9 varicella-related hospitalisations per 100,000 population from HIPE data in Ireland is consistent with reported incidence in countries without universal varicella vaccination programmes.[58, 59]

A UK study, conducted during the period from 2004 to 2017, reported an annual mean of 4,694 hospital admissions in England with a coding for varicella, with an estimated annual incidence rate of 8.9 admissions per 100,000 population.[60] The annual mean number of admissions over the study period was highest in the one to four years age group (n=2,336 admissions), representing 50% of all admissions.[60] A total of 38% of all admissions over the study period had a known complication of varicella, the most common being bacterial skin infections (11.4%), pneumonia (4.8%), febrile convulsions (3.4%) and encephalitis (2.4%).[60] The average complication rate was higher for those aged one to four years inclusive, at 41.9%.[60]

Varicella is long recognised as the number one risk factor for invasive Group A streptococcal (iGAS) disease, that includes skin and soft tissue infection with or without sepsis, necrotising fasciitis ('the flesh-eating bacteria') and streptococcal toxic shock-like syndrome.[61, 62] Prospective surveillance of iGAS in Ontario, Canada from 1992 to 1996, attributed a 58-fold increased risk of iGAS to varicella infection in the preceding two weeks.[61]. Over a 16-week period in 2016, 70% of a cluster of iGAS cases presenting to Children's Health Ireland at Temple Street had active chickenpox; sixty percent of cases required admission to the paediatric intensive care unit.[63] Reported case fatality rates range from 10% to 24% for necrotising fasciitis, and 36% to 56% for streptococcal toxic shock-like syndrome.[61, 64]

Since the beginning of October 2022, the Health Protection Surveillance Centre (HPSC) in Ireland has reported an increase in notified iGAS infections, compared with previous years, particularly in children under 10 years of age. Of the 179 iGAS cases notified between 2 October 2022 and 15 March 2023, 65 (36%) were in children less than 18 years of age, with 55 cases in those aged less than 10 years.[65] Increases in iGAS infection among young children have also been reported in France, the Netherlands, Sweden and the UK.[66-68] While the reasons for the increase in notified iGAS cases are not fully understood, a combination of factors may be contributing, including an increase in the circulation of respiratory viruses in the context of increased social mixing following the COVID-19 pandemic period. A number of recent reports also point to preceding viral infection, including varicella, as a potentially important risk factor for iGAS infection. [66-69]

## 3.4 Mortality

While death due to varicella is rare, it can and does occur. Since 2012, only one notified hospitalised case was reported as having died; this case was in the 55 to 64 year old age group, but the cause of death was recorded on CIDR as "not known".[70]

## 3.5 Treatment for varicella

Varicella is typically a mild self-limiting disease; treatment for the majority of cases is limited to supportive care (for example, paracetamol, skin emollients and topical or oral antihistamines.[71]) Antiviral medication (aciclovir, valaciclovir and famciclovir) may be beneficial for treating VZV infection and reducing the severity and duration of the disease with treatment recommendations differing based on the individual's risk of moderate and or severe disease. The Health Service Executive in Ireland advises that the value of antiviral medication for treating VZV infection in immunocompetent children is minimal, unless varicella is severe and treatment is initiated within 24 hours of the onset of the rash.[72] For immunocompetent adolescents and adults, who are at higher risk of severe varicella than young children, antivirals may be more beneficial in reducing the impact of the infection (lesions, fever and malaise). Antiviral treatment for this cohort should also be initiated within 24 hours of the appearance of the rash.[72, 73] Prompt intravenous antiviral therapy is recommended for individuals at high risk for severe disease and complications.[71]

## 3.6 Herpes zoster (shingles)

Primary infection with VZV results in varicella, after which the virus becomes latent in the body's nervous system. The virus may reactivate after a period, sometimes several decades later, resulting in herpes zoster (shingles). Herpes zoster usually starts with pain in the area of the nerve which is affected, followed by the development of a painful rash, usually affecting one side of the face or body.[4] The lifetime risk of developing herpes zoster is approximately 30%,[74] and 50% in people aged 85 years and over.[35] Someone with herpes zoster can transmit the VZV to someone who has not had varicella and is not immune, but someone with varicella cannot cause herpes zoster in another person. The household transmission rate of herpes zoster (to cause varicella) is estimated at 15%.[2]

Incidence of herpes zoster in the community in Ireland is estimated from data obtained from the sentinel surveillance programme for herpes zoster.[43] Between 2005 and 2019, at least 50% of herpes zoster notifications from sentinel general practices in Ireland related to adults aged at least 50 years old. For 2019 (provisional data), the most recent year that data are available, 62% of all herpes

zoster notifications from sentinel general practices, related to adults aged at least 50 years old. Relevant data from England and Wales reports that, prior to the introduction of herpes zoster vaccination programmes in both jurisdictions in 2013, the annual incidence of herpes zoster for those aged 70 to 79 years was estimated to be 790 to 880 cases per 100,000 people.[75]

Morbidity associated with herpes zoster increases with age and the most common complication is post-herpetic neuralgia; persistent pain (for more than 90 days after onset) in the area of the rash with the potential to cause significant reductions in quality of life, activity, mood and sleep.[76] At least 13% of people aged ≥60 years develop post herpetic neuralgia as a result of herpes zoster.[2] A 2015 systematic review of herpes zoster-associated mortality in Europe reported a case fatality rate of 61 per 100,000 cases (0.061%) in those aged ≥65 years compared with two per 100,000 cases (0.002%) in those aged 45-65 years.[77]

## 3.7 Economic burden of varicella

In considering the economic burden associated with varicella, both direct and indirect costs are relevant. Direct costs include those associated with medical care, for example, primary care visits, medication costs and hospitalisation costs. Indirect costs include productivity losses of both paid and unpaid work, for both patients who are ill and those providing care to those who are ill.

Studies examining the economic burden of varicella in Ireland are limited. A paper that evaluated hospital admissions for patients with primary varicella infection, estimated that varicella accounted for an average of 1,130 acute hospital and 161 ICU bed days annually in Irish hospitals. The associated annual cost for hospitalised varicella cases (n=266) only was estimated at €1.34 million.[57]

In the absence of universal varicella vaccination, the annual total economic burden associated with varicella in 31 countries across Europe has been estimated at over €650 million, with 65% attributable to productivity loss.[78] The same study estimated that the total cost of varicella disease in Ireland in 2018 was €7.74 million (based on 63,328 annual cases), of which €2.1 million was attributable to direct costs and €5.23 million was attributable to indirect costs.[78] This estimate included the cost of primary care visits (15% of total cost), hospitalisation (2%), prescription medication (5%), over-the-counter medication (5%), productivity loss for caregivers (63%) and productivity loss for patients (10%).[78] It should be noted that data used to generate these estimates were largely imputed from varicella burden of disease data from other European countries.[78]

## 3.8 Discussion

Varicella is a common, acute and highly contagious disease, affecting in excess of 50,000 people, mainly children, in Ireland each year. While typically a mild disease, complications occur, and for some cases primary care consultations, prescription medication, and or hospitalisation may be required. Following primary infection with VZV, those who have had varicella have a lifetime risk of 30% of developing herpes zoster in the future. Although limited research has been published examining the total economic burden of varicella in Ireland, estimates suggest that the burden, including both direct and indirect costs, is likely to be considerable.

# 4 Overview of reviews of the clinical efficacy and effectiveness of potential varicella vaccination strategies

## Key points

- A number of systematic reviews assessing the efficacy and effectiveness of varicella vaccines have been published over the last 40 years. Early reviews assessed the monovalent vaccine and a one-dose schedule, while more recent reviews assessed both the monovalent and quadrivalent MMRV vaccines and one- and two-dose schedules.
- An overview of reviews was undertaken to assess the current systematic review evidence of the clinical efficacy and effectiveness alternative varicella vaccination strategies.
- In total, 20 systematic reviews were included in the overview of reviews; 17 assessed the efficacy/effectiveness of one-dose strategies and 10 assessed the efficacy/ effectiveness of two-dose strategies.
- Based on estimates from reviews that conducted a meta-analysis, one-dose vaccination strategies (both monovalent and quadrivalent varicella vaccine types) are effective in preventing varicella of any severity, although effectiveness varied considerably, ranging from 67% efficacy up to 10 years after vaccination, to 88% effectiveness (follow-up period not reported).
- In outbreak settings specifically, one-dose effectiveness ranged from 54% nine to 10 years after vaccination to 98% at less than 3 years after vaccination.
- The evidence also suggests that one-dose vaccination strategies are highly effective against moderate to severe varicella with effectiveness estimates ranging from 90% to 100%.
- Evidence of waning immunity was most notable against varicella of any severity for one-dose strategies.
- Estimates of the effectiveness of two-dose varicella vaccination strategies (from reviews that conducted a meta-analysis) to prevent varicella of any severity were less variable, ranging from 87% to 95%, with similar estimates for outbreak settings. The evidence on the efficacy/effectiveness of two-dose

vaccination in preventing moderate and severe varicella was limited to a single review that reported 99% efficacy at ten years follow-up post vaccination.

- The main issues identified during the quality appraisal related to methodological flaws at the systematic review level rather than primary study level, and lack of detail in the reporting of reviews that restricted our analysis.
- Overall, there is clear and consistent evidence that vaccination is very effective at reducing varicella.

## 4.1 Introduction

The aim of this chapter is to review the clinical efficacy and effectiveness of potential varicella vaccination strategies.

## 4.2 Methods

A number of systematic reviews assessing the efficacy (a measure of how well vaccines work in a controlled trial)[79] and effectiveness (a measure of how well vaccines work in the real world)[79] of varicella vaccines have been published over the last 40 years, with early reviews based on the monovalent vaccine and a one-dose schedule, while more recent reviews are based on both the monovalent and quadrivalent MMRV vaccines and one- and two-dose schedules. The number and variety of systematic reviews reflect the evolution of varicella vaccination strategies since the development of the vaccine in the 1970s and the varying vaccination strategies currently evident between countries. However, no single existing systematic review captures the range of possible vaccination strategies across multiple outcomes. Therefore, in order to assess the clinical efficacy and effectiveness of potential varicella vaccination strategies, an overview of reviews was undertaken to produce a comprehensive and comprehensible summary of the relevant evidence generated since the development of the first live attenuated monovalent varicella vaccine almost 50 years ago.[80]

Many of the methods used to conduct a systematic review were applied to this overview of reviews. While guidance for conducting an overview of reviews continues to accumulate, recently published methodological guidance, Chapter V of Part I of the Cochrane Handbook for Systematic Reviews and Chapter 10 of the Joanna Briggs Institute's Manual for Evidence Synthesis, was used in the design and conduct of this review.[81-83]

### 4.2.1 Review protocol

This overview of reviews was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[84] and the protocol was registered with the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42022312325.

### 4.2.2 Research question

The specific question for this overview of reviews was developed to reflect the efficacy/effectiveness outcomes associated with varicella vaccination. The PICO (Population, Intervention, Comparator, Outcomes) framework used to formulate the research question is presented in Table 4.1.

**Table 4.1 Review inclusion and exclusion criteria**

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

### 4.2.3 Search strategy

A comprehensive electronic search was performed in Embase (Elsevier), Medline (EBSCO), the Cochrane Library and Google Scholar on 2 February 2022, with databases searched since inception. The SYSVAC and PROSPERO registries were also searched to identify relevant reviews and registered protocols for forthcoming systematic reviews. These searches were supplemented by a grey literature search of the Trip medical database, and the International Health Technology Assessment (HTA) database. Websites of health technology assessment (HTA) agencies and government health ministries from the countries ranked 1-50 in the Human Development Index,[85] and websites of a number of international health agencies, were searched. A full list of website domain names that were searched is provided in the supplementary file (Appendix A4.1). A non-domain specific Google search was also conducted. All search strings, developed in consultation with an information specialist, dates of searches and search results are provided in the supplementary file (Appendix A4.1). The references lists of included reviews were searched and forward citation searches of included reviews were conducted to identify additional relevant reviews. No date or language restrictions were applied.

### 4.2.4 Review selection, data extraction and management

Titles and abstracts of potentially eligible reviews were screened independently by two reviewers using Covidence software.[86] Full text reviews were independently assessed for eligibility by two reviewers according to the pre-specified inclusion and exclusion criteria outlined in Table 4.1. Any disagreements with screening or uncertain inclusions were resolved through discussion and with third party arbitration, when required. Data extraction for each review was conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements in screening, eligibility and data extraction were resolved through discussion and with third party arbitration, when required.

### 4.2.5 Assessment of methodological quality of included reviews

Two reviewers independently assessed the quality of each review using the AMSTAR 2 tool, “A MeaSurement Tool to Assess systematic Reviews, version 2”.[87] Disagreements were resolved by discussion and with third party arbitration, when required.

### 4.2.6 Data synthesis

Summary characteristics of included reviews and overall findings are presented in table format by dosing schedule. As this is an overview of reviews, findings that were extracted from the included reviews are synthesised narratively. The findings

are presented by dosing schedule, outcome and vaccine type, that is monovalent, quadrivalent MMRV and monovalent or quadrivalent (where the vaccine type was not specifically reported). Summary output figures were developed where appropriate. Given that the Preferred Reporting Items for Overviews of Reviews (PRIOR)[88] guidelines have not yet been published, the reporting of this overview adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.[84]

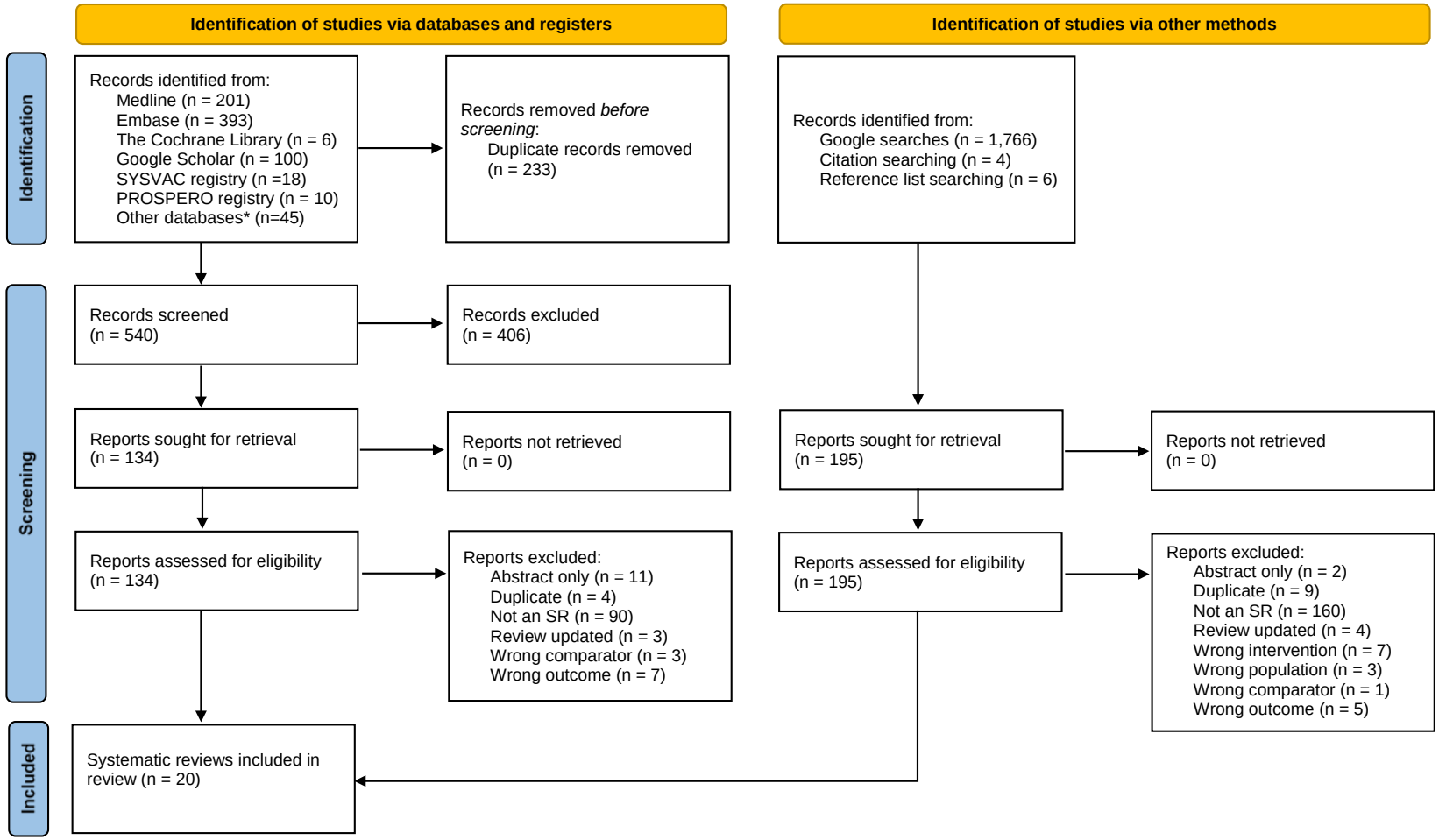
### 4.2.7 Overlap within included reviews

Overlaps of original research studies in each of the included reviews were identified, where possible. The level of overlap was determined by calculating the corrected covered area (CCA), a measure of overlap calculated by dividing the frequency of repeat occurrences of the index publication in other reviews by the product of index publications and reviews, reduced by the number of index publications.[89] A CCA of 0-5 indicates slight overlap, 6-10 moderate overlap, 11-15 high overlap and >15 very high overlap. [89]

## 4.3 Results

After removing duplicates, the initial search identified a total of 540 articles from databases and registers (n=497 articles) and grey literature sources (n= 43 articles). A total of 1,766 articles were identified from the initial google domain- and non-domain specific searches. After excluding articles based on title and abstract review, a total of 319 articles remained for full text review (n=134 from databases, registers and grey literature sources and n=185 from Google). Following full text review and subsequent exclusion, 17 systematic reviews remained for inclusion in this overview of reviews (n=16 from databases, registers and grey literature sources and n=1 from Google). An additional three eligible reviews were identified from reference checking (n=2) and forward citation searching (n=1) of included reviews, giving a final total of 20 eligible systematic reviews (Figure 4.1).

## Figure 4.1 PRISMA 2020 flow diagram of review selection




*TRIP database and International Health Technology Assessment database
Key: SR – systematic review;

### 4.3.1 Characteristics of included reviews

In total, 20 systematic reviews were identified that met the inclusion criteria for the review of efficacy and effectiveness of varicella vaccination. The most recent specified end search date within these reviews was September 2019.[90] Of the 20 reviews, five reviews included randomised controlled trials (RCTs) and observational studies[91-95] (including one[95] that also included four previously published systematic reviews); 13 reviews included observational studies only;[36, 90, 96-106] one review included four previously published systematic reviews and observational studies;[107] and the final review included two previously published systematic reviews.[108] Of the eight systematic reviews that were themselves included in eligible systematic reviews for this overview, only three met the pre-defined eligibility criteria for a systematic review and were therefore included in this overview.[94, 96, 97] Of the five reviews that did not meet the eligibility criteria, two included searches from one database only, search terms were not provided in another, the fourth and fifth were considered to be a seminar paper and position paper, respectively and not systematic reviews.

A total of ten of the 20 reviews that assessed efficacy/effectiveness provided a meta-analysis, five of which had no geographic limitation[91-93, 96, 97] (three of which included RCTs)[91-93] and five of which were based on primary observational studies from China only.[90, 98-101] The remaining ten reviews provided a narrative summary of findings, five of which had no geographic limitation[94, 95, 106-108] (three of which included RCTs)[94, 95, 107] and five that provided a synthesis of the experience with varicella vaccination specifically in Italy and Germany,[36] Central and Eastern Europe,[105] the Middle East,[102] Latin America and the Caribbean,[103] and the Asia-Pacific region.[104] Completed data extraction tables for all included reviews are provided in the supplementary file (Appendix A4.2).

### 4.3.2 Clinical efficacy/effectiveness of varicella vaccination

For ease of reading, the evidence in relation to the efficacy/effectiveness of varicella vaccination is presented in a number of separate sections. A narrative synthesis of the findings of this overview of reviews is presented by vaccine dose, outcome and vaccine type, that is monovalent, quadrivalent MMRV, and monovalent or quadrivalent (where the vaccine type was not clearly specified in the review).

The included systematic reviews variably reported vaccine effectiveness against ‘varicella of any severity’ and ‘all varicella’; for the purpose of this review, we have considered these to be synonymous and have used the term ‘varicella of any severity’ for consistency.

The 20 reviews that examined the efficacy/effectiveness of varicella vaccination included the following dosing strategies:

- seven reviews assessed one-dose only[94, 96, 98-100, 104, 105]
- one assessed two-dose only[90]
- nine assessed both one- and two-dose[36, 91, 97, 101-103, 106-108] (including four reviews that also provided some data relating to any-dose)[36, 91, 101, 107]
- two specifically assessed two- versus one-dose,[92, 93] with an additional review (already noted above) reporting limited data comparing two- and one-dose[107]
- one generally assessed any-dose,[95] with an additional four (already noted above) reporting some data relating to any-dose.[36, 91, 101, 107]

#### 4.3.2.1 One-dose varicella vaccination

A total of 17 reviews assessed the efficacy/effectiveness and or the impact of one-dose varicella vaccination, with eight reviews providing a meta-analysis[91, 93, 96-101] and nine reviews providing a narrative synthesis of findings.[36, 94, 102-108] The monovalent vaccine was assessed in five reviews, two that provided a meta-analysis[91, 97] and three narrative syntheses,[36, 103, 108] while the quadrivalent vaccine was assessed in two reviews,[91, 97] one of which provided a meta-analysis.[91] The vaccine type was not clear (that is, monovalent or quadrivalent) in 14 reviews; six reviews that provided a meta-analysis[93, 96, 98-101] and eight reviews that provided a narrative synthesis of findings[36, 94, 102-107] (including two reviews that reported the vaccine type in some countries reviewed but not in others). It should be noted that some reviews assessed multiple vaccine types. A summary of the characteristics of reviews that included a one-dose strategy is provided in Table 4.2, with a narrative summary of results by outcome and vaccine type provided below.

## Table 4.2 Summary characteristics for reviews that included one-dose varicella vaccination

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome measure | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| Al Kaabi 2020[102] | Individuals ≥12mths of age with breakthrough or primary varicella in the Middle East | NR | NR | Mostly NR: up to 5yrs in 1 study | Incidence of varicella; Hospitalisation and complications and hospitalisation associated with varicella; Long-term persistence of protection from varicella | Narrative synthesis | Although data on the impact of varicella vaccination in the Middle East are limited, the data that are available indicate that UVV has the potential to substantially reduce the clinical burden of the disease. | × | × | Critically Low |
| Arlant 2019[103] | Persons of any age and race in Latin America and the Caribbean who had primary and/or breakthrough varicella infection | Monovalent and NR | NR | Varied – up to 14yrs post UVV introduction | Costa Rica and Uruguay: Vaccine effectiveness against varicella; Incidence of varicella and breakthrough varicella; Ambulatory visits, hospitalisation, complications and mortality associated with varicella | Narrative synthesis | While there is a need for additional local data, current evidence in Latin American and the Caribbean, as described in this review, provides an impelling rationale for the wider implementation of vaccination in this region. | × | × | Critically Low |
| Bayer 2007[96]ǂ | Children, median aged 4mths-12yrs in outbreak settings | NR | NR | Unclear | Vaccine effectiveness against varicella | Meta-analysis | This meta-analysis confirms a limited effectiveness of 1-dose of varicella vaccine and points to waning immunity as an important causal factor. | × | × | Critically Low |
| Benchimol 2021[108] | Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy (associated systematic review based on the general population). | NR | NR | NR | Vaccine effectiveness against varicella | Narrative synthesis | Maintaining appropriate vaccination status in patients with IBD is critical to optimise patient outcomes. In general, live vaccines are recommended in patients not on immunosuppressive therapy, but not for those using immunosuppressive medications. | ✓ | ✓ | Critically Low |
| Di Pietrantonj 2021[91] | Healthy children aged up to 15yrs, or adults who received MMR or MMRV/MMR+V vaccination between 0 and 15yrs of age. | Monovalent (Varilrix®) AND Quadrivalent MMRV (ProQuad® and Priorix-Tetra®) | Yes – MMR | Up to 10yrs post vaccination | Vaccine efficacy and effectiveness against varicella | Meta-analysis | MMR+V and MMRV vaccines are effective in preventing the infection of children by chickenpox. | ✓ | ✓ | High |
| Garrido 2012[107] | Healthy children aged 1-12yrs at vaccination | NR | NR | Various | Vaccine effectiveness against varicella; Long-term persistence | Narrative synthesis | Considering the available evidence, it can be concluded that the varicella vaccine is an | × | ✓ | Critically Low |

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome measure | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | of protection from varicella | | effective intervention and safe in healthy children, not only because of the decrease in incidence but also in the associated morbidity and mortality. However, its implementation should be universal in order to allow a high coverage rate, and the possibility of two doses may be considered. | | | |
| Goh 2019[104] | Adults, infants, and children in the Asia Pacific region without evidence of immunity to VZV | NR | NR | Mostly NR; 10yrs for severe hospitalised varicella | Incidence of varicella; Hospitalisation, Complications and mortality associated with varicella | Narrative synthesis | Universal varicella vaccination programs have uniformly shown a reduction in varicella infection in those vaccinated. Hospitalisation rates were significantly decreased after access to varicella vaccine. | × | × | Critically Low |
| Hong 2017[98]‡ | Children and students in varicella clusters/outbreaks in China | NR | NR | <3-10yrs post vaccination | Vaccine effectiveness against varicella | Meta-analysis | Varicella vaccination has good vaccine effectiveness but decreases with time since vaccination in clusters/outbreaks. | × | × | Critically Low |
| Kaufmann 2020[36] | Persons who received varicella vaccination as part of a paediatric varicella vaccination program in Italy and Germany. | Monovalent in Italy<br><br>NR for Germany | NR | Italy: up to 4yrs after introduction of UVV<br>Germany: various including up to 10yrs post vaccination | <u>Italy:</u><br>Incidence of varicella; Hospitalisation and complications associated with varicella<br><u>Germany:</u><br>Vaccine effectiveness against varicella; Incidence of varicella; Hospitalisation and complications associated with varicella | Narrative synthesis | Substantial reductions in incidence of moderate/ severe varicella and varicella-related hospitalisation occurred during the 1-dose era.<br>Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively. | ✓ | × | Low |
| Marin 2016[97] | Immunocompetent children aged 12mths to 18yrs. (Outcomes predominantly calculated among preschool and elementary school-aged children). | Monovalent (various brands) AND Quadrivalent MMRV (Priorix-Tetra®) | NR | Varied - <10yrs likely median time since vaccination | Vaccine effectiveness against varicella | Meta-analysis | One-dose of varicella vaccine was moderately effective in preventing all varicella and highly effective in preventing moderate/severe varicella, with no differences by vaccine.<br>The second dose adds improved protection against all varicella. | × | × | Critically Low |

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome measure | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| Meszner 2019[105] | Males or females of any age and race who had primary and/or breakthrough varicella | NR | NR | NR | Incidence of varicella; Hospitalisation associated with varicella | Narrative synthesis | Limited data availability precludes an analysis of changes in varicella incidence following the introduction of vaccination in CEE. | × | × | Critically Low |
| New Zealand National Health Committee 2012[106] | Children aged 0-5yrs | NR | NR | Mostly NR: up to 10yrs post UVV introduction for hospitalisation associated with varicella | Vaccine effectiveness against varicella; Hospitalisation associated with varicella | Narrative synthesis | Evidence suggests that all single-antigen vaccines currently available for varicella are clinically safe and effective for most children aged 15mths and 4 years, alongside existing immunisations on the schedule. | × | × | Critically Low |
| Skull 2001[94] | Human subjects vaccinated with VZV vaccine | NR (likely to be monovalent given review date) | NR | Up to 7yrs | Vaccine efficacy/ effectiveness against varicella | Narrative synthesis | This critical review has found strong evidence for the effectiveness of VZV vaccination in the prevention of varicella in children. | ✓ | ✓ | Critically Low |
| Xu 2019[101]‡ | Children and students in varicella clusters/outbreaks in China | NR | NR | NR | Vaccine effectiveness against varicella | Meta-analysis | Varicella immunisation has a certain protective effect, which decreases with increasing vaccination age. | × | × | Critically Low |
| Zhang 2020[99] | Healthy children aged 1-12yrs in China | NR | NR | NR | Vaccine effectiveness against varicella | Meta-analysis | 1-dose in healthy children aged 1-12yrs in China can provide moderate protection against varicella, but the vaccine effectiveness of children ≥6yrs is significantly reduced. | ✓ | ✓ | Critically Low |
| Zhu 2018[93] | Breakthrough varicella cases in healthy children | Monovalent and quadrivalent; Various brands | Yes – MMR in 1 study | 14yrs after 1-dose; 10yrs after 2-dose | Incidence of breakthrough varicella | Meta-analysis | Two doses of varicella vaccine are more effective than a single dose, and 3-4 years between the first and second vaccinations may achieve higher efficacy. | ✓ | × | Critically Low |
| Zhu 2017[93] | Children aged 0-18yrs in China | NR | NR | NR | Vaccine effectiveness against varicella | Meta-analysis | Live attenuated varicella vaccine is moderately effective in preventing varicella, but vaccine effectiveness reduces over time. | ✓ | × | Critically Low |

‡ Outbreak settings
Key: AMSTAR2 - A MeaSurement Tool to Assess systematic Reviews, version 2; CEE – Central and Eastern Europe; IBD – inflammatory bowel disease; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; NR – not reported; SR – systematic review; UVV – universal varicella vaccination; VZV – varicella zoster vaccination;

#### 4.3.2.1.1 Efficacy and effectiveness in preventing varicella (any severity)

**Monovalent vaccine**

A meta-analysis of the efficacy/effectiveness of the monovalent vaccine in preventing varicella was conducted in two reviews.[91, 97] In the only review (Cochrane) assessed as 'high' quality using AMSTAR 2, the pooled efficacy of one-dose (Varilrix®) administered with the second dose measles-mumps-rubella (MMR) vaccine, against varicella of any severity, compared with MMR only, was estimated at 67% up to 10 years post vaccination (95% confidence interval [CI]): 64 to 70%, $I^2$=0%; 3 RCTs, n=approx. 3,000; high-certainty evidence [GRADE]).[91] This review also reported pooled effectiveness (from observational studies) of one-dose (multiple vaccine brands) administered with MMR, against varicella of any severity, compared with no varicella vaccination, of 86% (95% CI: 78 to 92%, $I^2$=0%; 2 case-control studies).[91] In a second review, a pooled estimate of vaccine effectiveness (multiple vaccine brands) against varicella of any severity, with a median time of less than 10 years since vaccination, was reported at 81% (95% CI: 78 to 84%, $I^2$ = 88%; 42 observational studies).[97]

**Quadrivalent MMRV vaccine**

The effectiveness of one-dose quadrivalent MMRV vaccine was limited to two reviews,[91, 97] with one providing a meta-analysis of vaccine effectiveness in preventing varicella.[91] The pooled vaccine effectiveness of one-dose quadrivalent MMRV (ProQuad® and Priorix-Tetra®) against varicella of any severity, compared with no vaccination, was 75% (95% CI: 41 to 89%, $I^2$=98%; 4 cohort studies).[91] Analysis by vaccine brand reported vaccine effectiveness of 94% (95% CI: 92 to 96%; 1 cohort study) for ProQuad® and 62% (95% CI: 61 to 63%; 3 cohort studies) for Priorix-Tetra®.[91] In a second review, vaccine effectiveness for Priorix-Tetra® was reported at 55% (95% CI: 8 to 78%; 1 cohort study) against varicella of any severity.[97]

**Monovalent or quadrivalent MMRV vaccine (vaccine type unclear)**

A number of reviews did not specifically report the type of vaccine used for a one-dose schedule, either for the review as a whole or for particular countries or regions reported within the review. This included a narrative review that reported vaccine efficacy in preventing varicella for a one-dose schedule of 100% (1 RCT) over nine months and 98% after seven years (although data after three years was subject to a large loss to follow-up), and 72% over a mean of 29 months in a second RCT (Level I evidence using the Canadian Task Force on Preventive Health Care methodology).[94] A cohort study included in the same review reported vaccine-

effectiveness of 83% in children less than five years old.[94] Given the timing of this review (search to December 2000), it is likely that the evidence relates to the monovalent vaccine, although this was not specified by the authors.

A total of five reviews conducted a meta-analysis of one-dose vaccine effectiveness in preventing varicella, compared with no vaccination, but did not provide detail on the type of vaccine administered.[96, 98-101] Of the five reviews, four included primary studies from China only.[98-101] All five reviews reported vaccine effectiveness in outbreak settings, either exclusively (n=3) or as part of further analysis. In two reviews, sub-group analyses were conducted with estimates reported for both younger and older children.[99, 100] In a third review, pooled estimates by time since vaccination were provided.[98] Overall, pooled estimates of one-dose vaccine effectiveness in these five reviews varied considerably and ranged from 54% (95% CI: -2 to 58%, $I^2$=0%; 2 cohort studies, n=464) in outbreak settings nine to 10 years post-vaccination in China,[98] to 98% (95% CI: 95 to 99%, $I^2$=38%; 2 cohort studies, n=1,033) ) in outbreak settings less than three years post-vaccination in China.[98] The results from these reviews are summarised in Table 4.3.

An additional four reviews provided a narrative synthesis of one-dose vaccine effectiveness against varicella. A review assessing the impact of one-dose vaccination in Germany reported vaccine-effectiveness of 86.6% (95% CI: 85.2 to 87.9) overall and 72% (95% CI: 59 to 81) in outbreaks in day care centres.[36] Similarly, the review covering Latin America and the Caribbean (LAC) reported vaccine effectiveness (from a single case-control study in regions of Brazil), against varicella of any severity, of 86% in children aged 15-35 months.[103] Two further reviews reported similar vaccine effectiveness for one-dose (versus no vaccination or placebo). In the first review, vaccine effectiveness was reported at 81% against varicella of any severity.[106] In the second review, it was reported at 80 to 85% for the prevention of any form of varicella (Level 1 and Level 2 evidence [SORT scale] from two systematic reviews).[107] Additionally, in outbreaks in primary schools, overall vaccine effectiveness for prevention of varicella, based on a meta-analysis of 14 studies, was reported at 72.5%, but varied considerably (20 to 100%) between studies.[107]

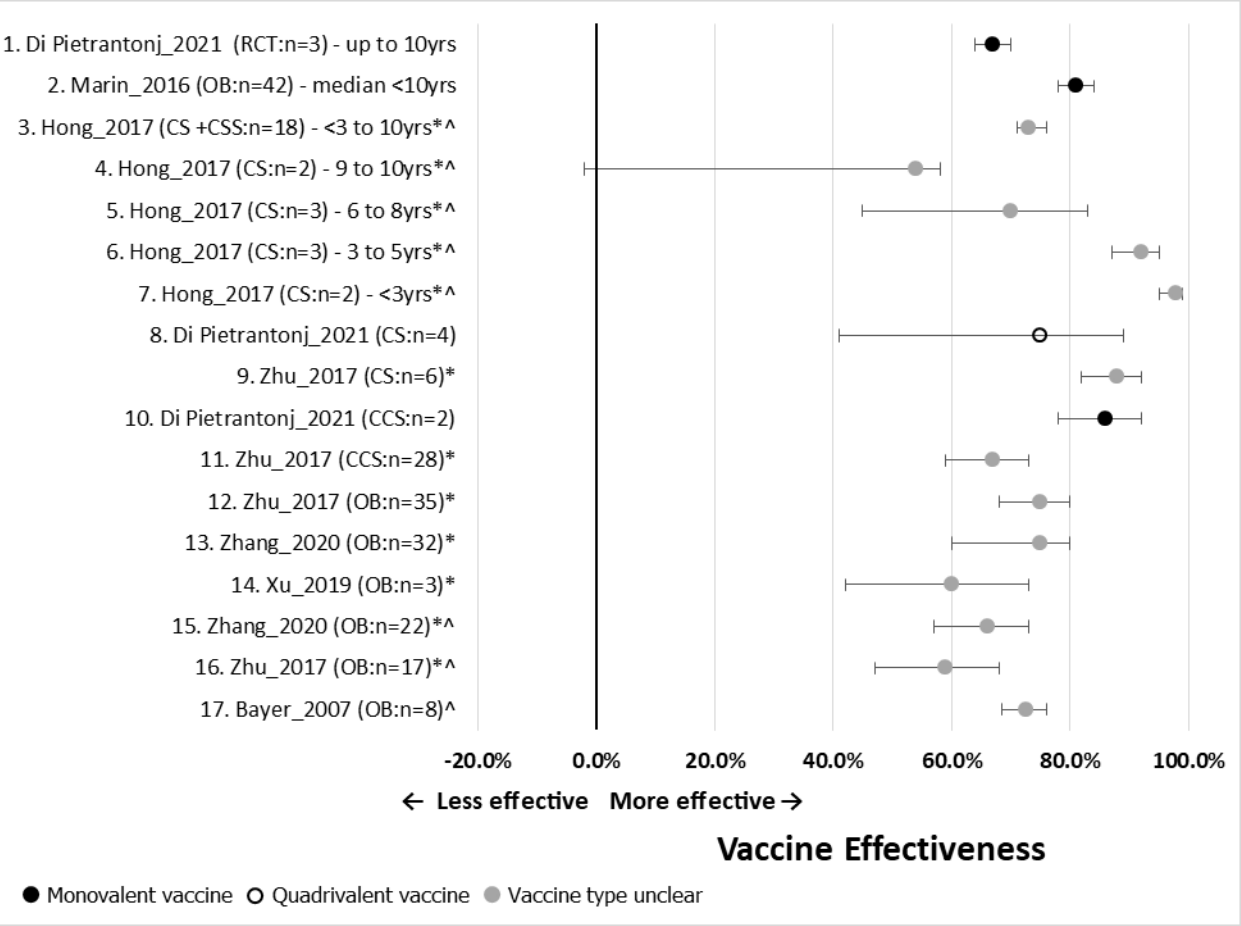
## Table 4.3 Summary of results from reviews that conducted a meta-analysis for one-dose vaccine effectiveness against varicella but didn't specify the vaccine type

| Review | Setting/ sub-group analysis | Vaccine Effectiveness (VE) | 95% CI, $I^2$ | Included Studies | Number of study participants | Certainty of Evidence | Additional Information |
|---|---|---|---|---|---|---|---|
| Zhang_2020[99] | Overall | 75% | 60 to 80%, 83% | n=32 observational studies | n=328,565 | GRADE: very-low | Study population from China only |
| | Outbreaks only | 66% | 51 to 73%, 62% | n=22 observational studies | n=17,154 | | |
| | Non-outbreak | 85% | 60 to 80%, 83% | n=10 observational studies | n=311,411 | | |
| | <6yrs old | 84% | 77 to 89%, 59% | n=12 observational studies | n=8,124 | | |
| | ≥6yrs old | 60% | 51 to 68%, 55% | n=19 observational studies | n=16,488 | | |
| Zhu_2017[100] | Overall | 75% | 68 to 80%, 90.7% | n=35 observational studies | n=421,189 | NR | Study population from China only |
| | Outbreaks only | 59% | 47 to 68%, NR | n=17 observational studies | n=13,352 | | |
| | Pre-school children | 90% | 81 to 95%, NR | n=10 observational studies | n=61,256 | | |
| | Primary school children | 67% | 52 to 78%, NR | n=17 observational studies | n=11,574 | | |
| | Cohort studies | 88% | 82 to 92%, NR | n=6 cohort studies | n=300,608 | | |
| | Case-control studies | 67% | 59 to 73%, NR | n=28 case-control cohort studies | n=119,443 | | |
| Bayer_2007[96] | Outbreaks only | 72.5% (substantial decrease in VE reported in follow-up from 6-72mths post vaccination) | 68.5 to 76%, NR | n=14 observational studies | n=3,157 | NR | Result reported in a 2nd review (Garrido) and assessed as Level I evidence (good-quality patient-oriented evidence [SORT scale]) |
| Hong_2017[98] | Outbreaks only: <3 to 10yrs post-vaccination | 73% | 71 to 76%, 22% | n=18 observational (case-control and cohort) studies | n=46,455 | NR | Study population from China only |
| | Outbreaks only: <3yrs post-vaccination | 98% | 95 to 99%, 38% | n=2 cohort studies | n=1,033 children aged 12mths-3yrs | | |
| | Outbreaks only: 3-5yrs post-vaccination | 92% | 87 to 95%, 58% | n=3 cohort studies | n=1,115 children aged 4-6yrs | | |
| | Outbreaks only: 6-8yrs post-vaccination | 70% | 45 to 83%, 17% | n=3 cohort studies | n=881 children aged 7-9yrs | | |
| | Outbreaks only: 9-10yrs post-vaccination | 54% | -2 to 58%, 0% | n=2 cohort studies | n=464 children and students | | |
| Xu_2019[101] | Outbreaks only | 60% | 42 to 73%, 31% | n=3 observational studies | NR | NR | Study population from China only |

Key: GRADE - Grading of Recommendations, Assessment, Development and Evaluations; SORT – Strength of Recommendation Taxonomy

Figure 4.2 provides a summary of estimates of pooled one-dose vaccine efficacy/effectiveness against varicella of any severity from reviews that conducted a meta-analysis. Study type, number of primary studies, follow-up period (if provided) and vaccine type are detailed for each review.

**Figure 4.2 Pooled vaccine efficacy/effectiveness (95% confidence interval) of one-dose varicella vaccination in preventing varicella of any severity (by estimate number, review, study type and follow-up)**




Comparator: The intervention for estimate number one was varicella vaccine + MMR vaccine and the comparator was MMR vaccine alone. For all other estimates, the comparator was no varicella vaccination.
*Review includes studies from China only
^Outbreak setting only
Key: CS – cohort study; CCS – case-control study; OB – observational study (study types not clear); RCT – randomised controlled trial

#### 4.3.2.1.2 Efficacy and effectiveness in preventing moderate and severe varicella

**Monovalent vaccine**

Vaccine efficacy for one-dose monovalent vaccination against moderate or severe varicella was reported at 90% (95% CI: 88 to 92%; 1 RCTs) at 10 year follow-up post vaccination and 95% (95% CI: 53 to 99%; 1 RCT) against severe varicella at between five and 10 years follow-up post vaccination.[91] In the only review that

conducted a meta-analysis, pooled vaccine effectiveness (from observational studies) for the prevention of moderate and severe varicella combined was estimated at 98% (95% CI: 97 to 99%, $I^2$ = 85%; 34 estimates), while the pooled estimate for the prevention of severe varicella was 100% (24 estimates).[97] A single narrative review reported vaccine effectiveness of 95 to 100% for the prevention of moderate to severe disease (Level 1 and Level 2 evidence [SORT scale] from two systematic reviews).[107]

**Quadrivalent MMRV vaccine**

In a single review, vaccine effectiveness for one-dose quadrivalent (Priorix-Tetra®) vaccination against severe varicella, was reported at 100% (1 cohort study).[97]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

One-dose vaccine effectiveness against moderate or severe disease was reported in two reviews where the vaccine type was not specified. In the first review, vaccine effectiveness of 97% was reported against moderate and severe varicella combined and 100% against severe varicella (17 studies in total).[106] In the second review, one-dose vaccine effectiveness was reported at 95 to 100% for the prevention of moderate to severe disease (Level 1 evidence [SORT scale] from one systematic review).[107]

#### 4.3.2.1.3 Incidence of breakthrough varicella

**Monovalent and quadrivalent vaccine (vaccine type unclear)**

A single review assessed the incidence of breakthrough varicella (BV) after one-dose varicella vaccination and included a meta-analysis.[93] In the period from 11 months to 14 years post-vaccination (mostly monovalent vaccine), the average pooled incidence rate of BV for one-dose was 8.5 cases per 1,000 person years (95% CI: 5.3 to 13.7, $I^2$=99.8%; 24 studies including RCTs, cohort and computer based/system studies from 12 countries, n=27,618 break-through cases).[93] In subgroup analysis, incidence of BV by age at vaccination was reported at 4.7 cases per 1,000 person years (95% CI: 2.2 to 9.8, $I^2$=99.9%; 13 study populations) in those aged ≤2 years at vaccination compared with 18.7 cases per 1,000 person years (95% CI: 10.7 to 32.8, $I^2$=98.1%; 6 study populations) in those aged >2 years at vaccination.[93] An analysis by time since vaccination reported incidence at 13.2 cases per 1,000 person years (95% CI: 7.2 to 24.08, $I^2$=96.4%; 14 study populations) in the first year after vaccination, rising to 28.0 (95% CI: 1.6 to 53.7, $I^2$=95.1%; 12 study populations) in the second year, falling to 15.0 (95% CI: 5.8 to 39.1, $I^2$=94.6%; 9 study populations) in the third year and rising again thereafter

until year eight (32.3 cases per 1,000 person years) (95% CI: 2.4 to 427.1, $I^2$=96.8%; 4 study populations) after vaccination (with a fall in year seven).[93]

#### 4.3.2.1.4 Impact on incidence of varicella

**Monovalent vaccine**

A narrative synthesis of individual country or regional experience since the introduction of one-dose monovalent vaccination programmes was provided in two reviews. The first review assessed the impact of one-dose monovalent universal varicella vaccination (UVV) programmes in Italy.[36] In a number of pilot regions, where regional implementation of UVV began in 2003, surveillance studies reported that incidence of varicella decreased by 30-80% depending on coverage rates.[36] The second review covered Latin America and the Caribbean and reported the experience of Costa-Rica (1 study) and Uruguay (3 observational studies) following introduction of routine varicella vaccination with the monovalent vaccine.[103] In Costa Rica, reductions of 74% in varicella cases in the total population and 79% in children less than five years old were reported seven years after the introduction of UVV; vaccination coverage of 95% was reported in 2015 (eight years after the introduction of UVV).[103] In Uruguay, incidence of varicella was reported at 20/100,000 population ten years after UVV introduction; coverage of 90% was reported soon after UVV introduction in 1999. However, in one outbreak reported, 97% of varicella cases were among vaccinated children.[103]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

The impact of one-dose vaccination on incidence of varicella in Germany, Central and Eastern Europe , the Middle East, Latin America and the Caribbean, and the Asia-Pacific region, was reported in five reviews, but the type of vaccine used was not stated. The first review assessing the experience with one-dose UVV in Germany reported that surveillance studies have reported decreased incidence of 63 to 75% in children less than four years old. [36] A broader geographic review also noted evidence from a sentinel dataset from Germany demonstrating a reduction in incidence of varicella in four consecutive seasons following the introduction of UVV, and while the decrease was greatest in 0-4yr olds, the trend was seen in all age groups.[106]

In the review covering Central and Eastern Europe, it is noted that data on the impact of the introduction of varicella vaccination, including the introduction of a one-dose schedule in Latvia in 2008, are limited and therefore preclude an analysis of changes in incidence of varicella.[105] In the third review reporting on the Middle East, the experience of Turkey is reported from ten observational studies.[102] Comparing those vaccinated to those not vaccinated, the incidence of varicella was lower in vaccinated children aged two to 15.5 years old.[102] However, risk of

varicella was 3.5 times higher in children vaccinated at least five years previously compared to those vaccinated more recently.[102] The review of Latin America and the Caribbean also reported reductions in incidence of varicella in the Florianapolis and Sao Paulo areas of Brazil after the introduction of one-dose vaccination. [103]

Lastly, in the review covering the Asia-Pacific region, a 2.9 to 3.8 fold reduction in incidence of varicella was reported in Taiwan (3 studies), while an increase in incidence was reported in Australia and South Korea, when the pre- and post-UVV eras were compared.[104] In the case of Australia, where a coverage rate of 78.4% was reported two years after the introduction of UVV, the authors reported that the apparent low number of cases highlights that there are possibly issues with under reporting, impacting on the reliability of the data.[104] It was also reported that the Korean Centers for Disease Control and Prevention did not begin reporting varicella incidence until the introduction of UVV (in 2005) and the rise in cases from 2005 to 2009 likely reflect the impact of the introduction of varicella notification rather than increase in incidence. However, while a decline in incidence was seen in 2010, further rises have been seen in a number of years up to 2016; UVV coverage was reported at 97% in 2011.[104]

#### 4.3.2.1.5 Impact on ambulatory visits, complications, hospitalisation and morbidity associated with varicella

**Monovalent vaccine**

In the review assessing the impact of one-dose monovalent UVV in Italy, reductions in varicella-related hospitalisation (numbers not reported) were seen in three Italian regions, with decreases of 44% and 26% seen in two further regions within four years of introduction of UVV.[36] A single study in this review also reported a decrease in complications associated with varicella in Sicily, from 57 cases in 2002 to 14 in 2007 (four years after the introduction of UVV).[36] The review covering Latin America and the Caribbean reported that hospitalisations associated with varicella and hospitalisations for complicated varicella fell by 86% and 98%, respectively in Costa Rica when the pre- and post- UVV eras were compared; coverage rates of 76% and 95% were reported one year and seven years after UVV introduction respectively.[103] In Uruguay, ambulatory visits (recorded by private insurance companies) and hospitalisations associated with varicella were reported to have fallen by 87% and 81%, respectively within six years of UVV introduction; a coverage rate of 90% was reported soon after UVV introduction and was maintained up to 2013.[103] Additionally, in the period from two years before, to six years after UVV introduction in Uruguay, 7% of those with breakthrough varicella had complications, compared with 12% in those who were unvaccinated.[103]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

The review reporting the experience of one-dose UVV in Germany noted that over a six year period following the introduction of UVV, hospitalisations associated with varicella decreased by 65%.[36] Reductions were greatest in those cohorts aged less than one year and aged one to four years old. An epidemiological study reported that complications associated with varicella decreased in all age groups from 0.4% in the first season of UVV to 0.2% by the fourth UVV season. [36]

The review from the Asia-Pacific region reported that data on hospitalisation associated with varicella for Taiwan were limited and varied; while admission rates for those with varicella are reported to have fallen after UVV introduction and the proportion of patients with neurological complications significantly reduced, dermatological admissions due to varicella increased.[104] In Australia, reductions in hospitalisation associated with varicella were reported after the introduction of one-dose UVV (coverage rate of 78.4% reported two years after UVV introduction), while in a 10 year follow-up study, vaccinated children were less likely to have severe hospitalised varicella (length of stay >7 days and or intensive care unit management).[104] In the review covering the Middle East, the experience of Turkey is reported from ten observational studies. Comparing those vaccinated with those not vaccinated, the incidence of complications with varicella in non-hospitalised children in an outbreak was lower in vaccinated children; incidence of hospitalisation with varicella for children aged one to five years was also lower in the vaccinated cohort.[102] A geographically broader review also noted evidence from five studies of reductions in hospitalisation associated with varicella in Australia, Germany and the USA following the introduction of UVV.[106]

The review from the Asia-Pacific region noted a single study in Taiwan that reported no difference in case-fatality rates when the pre- and post-UVV eras were compared, while a second study reported a lower fatality rate in the post vaccine era.[104] The review covering LAC reported no difference in mortality associated with varicella after UVV introduction in Costa Rica.[103] One further review, focused mainly on an assessment based on any-dose varicella vaccination, reported that during the 12 years of the mostly one-dose programme in the US, the average age-adjusted mortality due to varicella as an underlying cause of death decreased 88% to 0.05 per1 million population during the period 2005–2007, with a reduction of 97% among persons aged less than 20 years.[95]

#### 4.3.2.2 Two-dose varicella vaccination

A total of ten reviews assessed the efficacy/effectiveness and or the impact of a two-dose varicella vaccination schedule, with four reviews providing a meta-analysis[90, 91, 97, 101] and six reviews providing a narrative synthesis of findings.[36, 102, 103, 106-108] The monovalent vaccine was assessed in two meta-analyses[91, 97] and one narrative

syntheses,[103] while the quadrivalent vaccine was assessed in two reviews,[91, 97] one of which conducted a meta-analysis.[91] The vaccine type was not clear in eight reviews; two reviews that conducted a meta-analysis[90, 101] (both reviews included studies from China only) and five reviews that provided a narrative synthesis of findings[36, 102, 106-108] (including two reviews that reported the vaccine type used in some countries reviewed, but not in others). It should be noted that some reviews assessed multiple vaccine types. A summary of the characteristics of reviews that included a two-dose strategy is provided in Table 4.4, with a narrative summary of results by outcome and vaccine type provided below.

## Table 4.4 Summary characteristics for reviews that included two-dose varicella vaccination

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| Al Kaabi 2020[102] | Individuals ≥12mths of age with breakthrough or primary varicella in the Middle East | NR | NR | NR | Incidence of varicella; | Narrative synthesis | Although data on the impact of varicella vaccination in the Middle East are limited, the data that are available indicate that UVV has the potential to substantially reduce the clinical burden of the disease. | × | × | Critically Low |
| Arlant 2019 | Persons of any age and race in Latin America and the Caribbean who had primary and/or breakthrough varicella infection | Monovalent | NR | Varied - up to 17yrs post UVV introduction for morbidity associated with varicella | Mortality associated with varicella | Narrative synthesis | While there is a need for additional local data, current evidence in Latin American and the Caribbean, as described in this review, provides an impelling rationale for the wider implementation of vaccination in this region. | × | × | Critically Low |
| Benchimol 2021[108] | Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy (associated systematic review based on the general population). | NR | NR | NR | Vaccine effectiveness against varicella | Narrative synthesis | Maintaining appropriate vaccination status in patients with IBD is critical to optimise patient outcomes. In general, live vaccines are recommended in patients not on immunosuppressive therapy, but not for those using immunosuppressive medications. | ✓ | ✓ | Critically Low |
| Di Pietrantonj 2021[91] | Healthy children aged up to 15yrs, or adults who received MMR or MMRV/MMR+V vaccination between 0 and 15yrs of age. | Monovalent (Varivax® and other) AND quadrivalent MMRV (ProQuad® and Priorix-Tetra®) | Yes – MMR | Up to 10yrs post vaccination | Vaccine efficacy and effectiveness against varicella | Meta-analysis | MMR+V and MMRV vaccines are effective in preventing the infection of children by chickenpox. | ✓ | ✓ | High |
| Garrido 2012[107] | Healthy children aged 1-12yrs at vaccination | NR | NR | Various | Vaccine effectiveness against varicella; Long-term persistence of protection from varicella | Narrative synthesis | Considering the available evidence, it can be concluded that the varicella vaccine is an effective intervention and safe in healthy children, not only because of the decrease in incidence but also in the associated morbidity and mortality. However, its implementation should be universal in order to allow a high coverage rate, and the | × | ✓ | Critically Low |

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | possibility of two doses may be considered. | | | |
| Kaufmann 2020[36] | Persons who received varicella vaccination as part of a paediatric varicella vaccination program in Italy and Germany. | Monovalent and NR | NR | Italy: up to 4yrs after introduction of UVV<br>Germany: various including up to 10yrs post vaccination | Vaccine effectiveness against varicella including interval between vaccines and age at vaccination; Incidence of varicella; Hospitalisation associated with varicella | Narrative synthesis | Substantial reductions in incidence of moderate/ severe varicella and varicella-related hospitalisation occurred during the 1-dose era.<br>Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively. | ✓ | × | Low |
| Marin 2016[97] | Immunocompetent children aged 12mths to 18yrs. (Outcomes predominantly calculated among preschool and elementary school-aged children). | Monovalent (various brands) AND Quadrivalent MMRV (Priorix-Tetra®) | NR | Varied - <10yrs likely median time since vaccination | Vaccine effectiveness against varicella | Meta-analysis | One dose of varicella vaccine was moderately effective in preventing all varicella and highly effective in preventing moderate/severe varicella, with no differences by vaccine.<br>The second dose adds improved protection against all varicella. | × | × | Critically Low |
| New Zealand National Health Committee 2012[106] | Children aged 0-5yrs | NR | NR | Mostly NR: up to 10yrs post UVV introduction for hospitalisation associated with varicella | Vaccine effectiveness against varicella; Hospitalisation associated with varicella | Narrative synthesis | Evidence suggests that all single-antigen vaccines currently available for varicella are clinically safe and effective for most children aged 15mths and 4 years, alongside existing immunisations on the schedule. | × | × | Critically Low |
| Xu 2019[101]‡ | Children and students in varicella clusters/outbreaks in China | NR | NR | NR | Vaccine effectiveness against varicella | Meta-analysis | Varicella immunisation has a certain protective effect, which decreases with the increase of vaccination age. | × | × | Critically Low |
| Zhang 2021[90] | Healthy children aged 2-12yrs in China | NR except Beijing Tiantan Biological Products Corp. Ltd. for 1 study | NR | NR | Vaccine effectiveness against varicella | Meta-analysis | Available data from China showed that the VE of the two-dose varicella vaccine is relatively high. | ✓ | ✓ | Critically Low |

‡ Outbreak settings
Key: AMSTAR2 - A MeaSurement Tool to Assess systematic Reviews, version 2; IBD – inflammatory bowel disease; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; NR – not reported; SR – systematic review; UVV – universal varicella vaccination; VZV – varicella zoster vaccination;

#### 4.3.2.2.1 Efficacy/effectiveness in preventing varicella (any severity)

**Monovalent vaccine**

A meta-analysis of the effectiveness of two-dose monovalent vaccination in preventing varicella was conducted in two reviews. In the only review assessed as 'high' quality using AMSTAR 2, the pooled estimate of vaccine effectiveness of two-dose monovalent varicella (multiple vaccine types) administered with MMR, against varicella of any severity, compared with no varicella vaccination, was 95% (95% CI: 86 to 99%, $I^2$=0%; 2 case-control studies).[91] In a second review, the pooled estimate of vaccine effectiveness against varicella of any severity was 92% (95% CI: 88 to 95%, $I^2$ = 57%; 4 cohort and 4 case-control studies).[97]

**Quadrivalent vaccine**

The efficacy or effectiveness of two-dose quadrivalent MMRV vaccination in preventing varicella was reported in two reviews. In the only review (Cochrane) assessed as 'high' quality using AMSTAR 2, the efficacy of two-dose quadrivalent MMRV (Priorix-Tetra®) against varicella of any severity at 10 year follow-up post vaccination, compared with MMR vaccination only, was reported at 95% (95% CI: 94 to 96%; 1 RCT, n=approx. 3,000; high-certainty evidence [GRADE]).[91] The same review reported pooled vaccine effectiveness (Priorix-Tetra®) against varicella of any severity, compared with no vaccination, of 87% (95% CI: 86 to 87%, $I^2$=0%; 2 cohort studies), while a second review reported vaccine effectiveness (Priorix-Tetra®) of 91% (95% CI: 65 to 98%; one cohort study) against varicella of any severity.[97]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

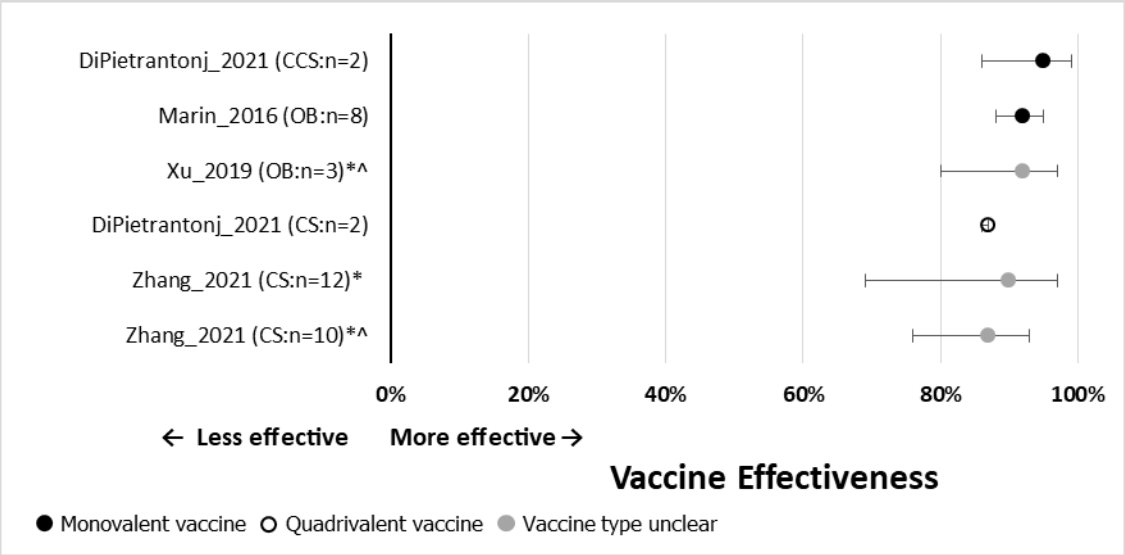
A meta-analysis of studies from China only reported a pooled vaccine effectiveness of two-dose vaccination (vaccine type not reported) against varicella, compared with no vaccination, of 90% (95% CI: 69 to 97%, $I^2$=83%; 12 cohort studies, n=87,196; low quality evidence [GRADE]).[90] In the same review, vaccine effectiveness in outbreak settings was reported at 87% (95% CI: 76 to 93%, $I^2$=0%; 10 cohort studies, n=3,636) and 99% in non-outbreak settings (95% CI: 98 to 99%, $I^2$=34%; 2 cohort studies, n=83,560).[90] A second review that conducted a meta-analysis of studies in varicella clusters/outbreaks in China, reported a pooled vaccine effectiveness, compared with no vaccination, of 92% (95% CI: 80 to 97%, $I^2$=0%; 3 studies).[101]

A total of four reviews that provided a narrative synthesis of findings reported vaccine effectiveness for two-dose vaccination. In one review, a pooled two-dose vaccine effectiveness of 92% (95% CI: 88 to 95%), against varicella of any severity,

was reported.[108] In a second review, two-dose vaccine effectiveness of 98.3% (95% CI: 97.3 to 99%; 1 systematic review) was reported over an observational period of up to 10 years post vaccination and was assessed as Level II evidence (limited-quality patient-oriented evidence [SORT scale]).[107] A similar vaccine effectiveness of 98% (from 17 studies), against varicella of any severity, was reported in a third review.[106] A narrative review of the experience in Germany reported vaccine effectiveness against varicella of 97.3% (95% CI: 85.2 to 87.9) covering the five year period from implementation of the two-dose strategy and was based on one nationwide surveillance study of health insurance claims data.[36] The review also reported results from one study that two-dose vaccine effectiveness for all combinations of monovalent varicella and quadrivalent MMRV vaccines ranged between 94.3% (95% CI: 93.9 to 94.8) and 95.0% (95% CI: 94.3 to 95.5), noting that the type of vaccine administered and the order do not influence effectiveness.[36] Lastly, the review reported that vaccine effectiveness was not impacted by either age at first vaccination (<15 months versus ≥15 months; one matched case-control study) or the interval between first and second dose (range 28 days to three years; one surveillance study).[36]

Figure 4.3 provides a summary of estimates of pooled two-dose vaccine effectiveness for varicella of any severity from reviews that conducted a meta-analysis. Study type, the number of primary studies and the vaccine type are detailed for each included review.

**Figure 4.3 Pooled vaccine effectiveness (95% confidence interval) of two-dose varicella vaccination in preventing varicella of any severity (by review and study type)**




Comparator: The comparator for all estimates was no vaccination
*Review includes studies from China only
^Outbreak setting only
Key: CS – cohort study; CCS – case-control study; OB – observational study (study type not clear);

#### 4.3.2.2.2 Efficacy/effectiveness in preventing moderate or severe varicella

**Quadrivalent vaccine**

The efficacy of two-dose quadrivalent MMRV vaccination in preventing moderate or severe varicella at 10 year follow-up post vaccination, was reported at 99% in one RCT (95% CI: 98 to 100%; n=approx. 3,000; high-certainty evidence [GRADE]).[91]

#### 4.3.2.2.3 Impact on incidence of varicella

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

The narrative review assessing the experience of two-dose UVV in Germany and eight Italian regions reported a three to four fold decrease in the incidence of varicella infection in Germany (from surveillance studies and other data sources) following the implementation of a two-dose strategy.[36] Pooled analysis of epidemiological data from all eight Italian regions demonstrated significant reductions in incidence of varicella up to nine years after UVV introduction. [36] In Sicily alone, varicella notifications decreased by over 95% between 2003 (when the two-dose schedule was introduced) and 2012.[36] In the review covering the Middle East, the impact of 2-dose varicella vaccination in both Abu Dhabi in the United Arab Emirates and Saudi Arabia were reported.[102] Comparing pre- and post-UVV periods, incidence of varicella fell from 486 (2011) to between 147 and 168 (2013) per

100,000 population (65 to 70% reduction) in Abu Dhabi and from 739.8 (1994) to 88.1 (2011) per 100,000 population (88% reduction) in Saudi Arabia.[102]

#### 4.3.2.2.4 Impact on complications, hospitalisation, morbidity and mortality associated with varicella

**Monovalent vaccine**

The review of Latin America and the Caribbean reported a substantial decrease in morbidity associated with varicella in Puerto Rico following the introduction of two-dose UVV. Morbidity rates fell from 11.6 cases in 1998 to 2.8 cases per 100,000 population in 2015 (1 study).[103] The vaccination strategy changed from one-dose monovalent in 1996 to a two-dose strategy from 2007; however, disaggregated data for the one-dose strategy were not reported.

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

Following the introduction of two-dose UVV in both Germany and eight Italian regions, reductions in varicella related hospitalisations were reported.[36] In Germany, where two-dose UVV was introduced in 2009, national hospital discharge data showed that the mean age-adjusted incidence of varicella-related hospitalisations decreased from 3.3 to 1.9 per 100,000 person years after UVV introduction (2005-2012 period), with the highest declines observed in regions with the highest vaccination coverage.[36] Pooled analysis of epidemiological data from all eight regions of Italy that introduced two-dose UVV from 2005, showed a substantial reduction in rates of hospitalisation associated with varicella by 2012.[36]

### 4.3.2.3 Two- versus one- dose varicella vaccination

A total of three reviews assessed the efficacy/effectiveness of two- versus one-dose vaccination. A meta-analysis was conducted in two reviews,[92, 93] with a further review providing a narrative synthesis of findings.[107] A summary of the characteristics of reviews that included two- versus one-dose vaccination is provided in Table 4.5, with a narrative summary of results by outcome and vaccine type provided below.

## Table 4.5 Summary characteristics for reviews that included two- versus one-dose varicella vaccination

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome measures | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| Garrido 2012[107] | Healthy children aged 1-12yrs at vaccination | NR | NR | Various | Incremental vaccine effectiveness (2-dose versus 1-dose) | Narrative synthesis | Considering the available evidence, it can be concluded that the varicella vaccine is an effective intervention and safe in healthy children, not only because of the decrease in incidence but also in the associated morbidity and mortality. However, its implementation should be universal in order to allow a high coverage rate, and the possibility of two doses may be considered. | × | ✓ | Critically Low |
| Yin 2018[92] | Immunocompetent children aged 12mths to 12yrs in USA and 10 European countries | NR | NR | 3-10yrs for vaccine efficacy | Incremental vaccine efficacy/effectiveness (2-dose v 1-dose) against varicella | Meta-analysis | Two-dose vaccination provides superior protection against breakthrough varicella infection compared to one-dose vaccination. | ✓ | × | Critically Low |
| Zhu 2018[93] | Breakthrough varicella cases in healthy children | Monovalent and quadrivalent; Various brands | Yes – MMR in 1 study | 14yrs after 1-dose; 10yrs after 2-dose | Incidence of breakthrough varicella | Meta-analysis | Two doses of varicella vaccine are more effective than a single dose, and 3-4 years between the first and second vaccinations may achieve higher efficacy. | ✓ | × | Critically Low |

Key: AMSTAR2 - A MeaSurement Tool to Assess systematic Reviews, version 2; MMR – measles, mumps, rubella; NR – not reported; SR – systematic review;

#### 4.3.2.3.1 Efficacy/effectiveness in preventing varicella

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

A single review specifically examined incremental vaccine effectiveness, defined as the additional reduction in varicella disease experienced by two-dose vaccine recipients, relative to one-dose recipients, and conducted a meta-analysis.[92] The pooled incremental efficacy of two-dose versus one-dose vaccination in preventing varicella was 79% (95% CI: 56 to 90%, $I^2$=91.4%; 2 RCTs) and the pooled incremental effectiveness was 81% (95% CI: 65 to 90%, $I^2$=26.4%; n=1,547, 5 case-control studies).[92] In the RCT analysis, the interval between doses was reported as three weeks to six months, with follow-up between three and ten years post vaccination.[92] The review also reported pooled incremental vaccine effectiveness in outbreak settings (day care centres and schools) of 63% (95% CI: 36 to 79%, $I^2$=54.6%; n=2,389, 7 retrospective cohort studies); 42% for laboratory-confirmed varicella (95% CI: -0.01 to 67%, $I^2$=59.5%; 2 retrospective cohort studies) and 80% for clinically diagnosed varicella (95% CI: 62 to 90%, $I^2$=0%; 5 retrospective cohort studies).[92]

#### 4.3.2.3.2 Incidence of breakthrough varicella

**Monovalent and quadrivalent vaccine (vaccine type unclear)**

A single review assessed the incidence of breakthrough varicella (BV) after both one- and two-dose varicella vaccination and included a meta-analysis.[93] In the period from 11 months to 14 years post-vaccination (mostly monovalent vaccine), the average pooled incidence rate of BV for one-dose was 8.5 cases per 1,000 person years (95% CI: 5.3 to 13.7, $I^2$=99.8%; 24 studies including RCTs, cohort and computer based/system studies from 12 countries, n=27,618 break-through cases).[93] This compared with a rate of 2.2 cases per 1,000 person years for two-dose (95% CI: 0.5 to 9.3, $I^2$=86.3%; 5 studies including RCTs and cohort studies from 6 countries, n=24 breakthrough cases) in the period from 10.5 months to 10 years post-vaccination (monovalent and quadrivalent vaccines).[93] A second review reported results from another systematic review that compared one- and two-dose schedules and concluded that two-dose recipients had a 3.3 fold lower risk of breakthrough varicella.[107]

### 4.3.2.4 Any-dose (at least one-dose) varicella vaccination

A total of five reviews assessed the efficacy or effectiveness and or the impact of the varicella vaccine without specifying the dosing schedule. A meta-analysis was conducted in two reviews,[91, 101] with three further reviews providing a narrative synthesis of findings.[36, 95, 107] In addition to uncertainty around the number of

doses, the vaccine type was also not clear in four of the five reviews; this included one review that provided a meta-analysis of studies from outbreak settings in China only[101] and the three reviews that provided a narrative synthesis of findings.[36, 95, 107] It should be noted that some reviews assessed multiple vaccine types. A summary of the characteristics of reviews that included any-dose of the vaccine is provided in Table 4.6, with a narrative summary of results by outcome and vaccine type provided below.

## Table 4.6 Summary characteristics for reviews that included any-dose varicella vaccination

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| Di Pietrantonj 2021[91] | Healthy children aged up to 15yrs, or adults who received MMR or MMRV/MMR+V vaccination between 0 and 15yrs of age. | Monovalent (Varivax® and other) AND Quadrivalent MMRV (Priorix-Tetra® and other) | Yes – MMR | Up to 10yrs post vaccination | Vaccine effectiveness against varicella and hospitalisation associated with varicella. | Meta-analysis | MMR+V and MMRV vaccines are effective in preventing the infection of children by chickenpox. | ✓ | ✓ | High |
| Garrido 2012[107] | Healthy children aged 1-12yrs at vaccination | NR | NR | Various | Vaccine effectiveness against varicella;<br>Long-term persistence of protection from varicella | Narrative synthesis | Considering the available evidence, it can be concluded that the varicella vaccine is an effective intervention and safe in healthy children, not only because of the decrease in incidence but also in the associated morbidity and mortality. However, its implementation should be universal in order to allow a high coverage rate, and the possibility of two doses may be considered. | × | ✓ | Critically Low |
| Kaufmann 2020[36] | Persons who received varicella vaccination as part of a paediatric varicella vaccination program in Italy and Germany. | Monovalent and NR | NR | Italy: up to 4yrs after introduction of UVV<br>Germany: various including up to 10yrs post vaccination | <u>Italy:</u><br>Incidence of varicella;<br>Hospitalisation and complications associated with varicella<br><u>Germany:</u><br>Vaccine effectiveness against varicella;<br>Incidence of varicella;<br>Hospitalisation and complications associated with varicella | Narrative synthesis | Substantial reductions in incidence of moderate/ severe varicella and varicella-related hospitalisation occurred during the 1-dose era. Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively. | ✓ | × | Low |
| Pallas 2012[95] | Human subjects vaccinated with VZV vaccine | NR | NR except MMR for risk of breakthrough varicella | Various incl. NR<br>4-10yrs (incidence)<br>5-15yrs (hospitalisation) | Vaccine effectiveness against varicella;<br>Incidence of (breakthrough) varicella;<br>Hospitalisation and complications associated with varicella;<br>Mortality associated with varicella | Narrative synthesis | The safety and effectiveness of monovalent varicella vaccines and quadrivalent MMRV vaccines seem to be supported sufficiently by a large amount of evidence. However, due to large heterogeneity between studies, it is often difficult to summarise the evidence. | × | × | Critically Low |
| Xu | Children and students | NR | NR | NR | Vaccine effectiveness | Meta- | Varicella immunisation has a | × | × | Critically |

| Author and Year | Population | Vaccine type (brand) | Concurrent administration with another vaccine | Duration of follow-up | Main outcome | Type of synthesis | Authors overall conclusion | Risk of bias conducted | Overall quality of evidence conducted | AMSTAR 2 Rating for SR |
|---|---|---|---|---|---|---|---|---|---|---|
| 2019[101]‡ | in varicella clusters/outbreaks in China | | | | against varicella | analysis | certain protective effect, which decreases with increasing vaccination age. | | | Low |

‡ Outbreak settings
Key: AMSTAR2 - A MeaSurement Tool to Assess systematic Reviews, version 2; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; MMR+V – concurrent administration of measles, mumps, rubella vaccine and varicella vaccine; NR – not reported; SR – systematic review; UVV – universal varicella vaccination; VZV – varicella zoster vaccination;

#### 4.3.2.4.1 Efficacy / effectiveness in preventing varicella

**Monovalent vaccine**

The pooled vaccine effectiveness of at least one-dose monovalent vaccine (multiple brands) administered with the MMR vaccine, versus MMR only, against varicella of any severity, was estimated at 88% (95% CI: 82 to 92%, $I^2$=0%; 2 case-control studies) in one review.[91]

**Quadrivalent MMRV vaccine**

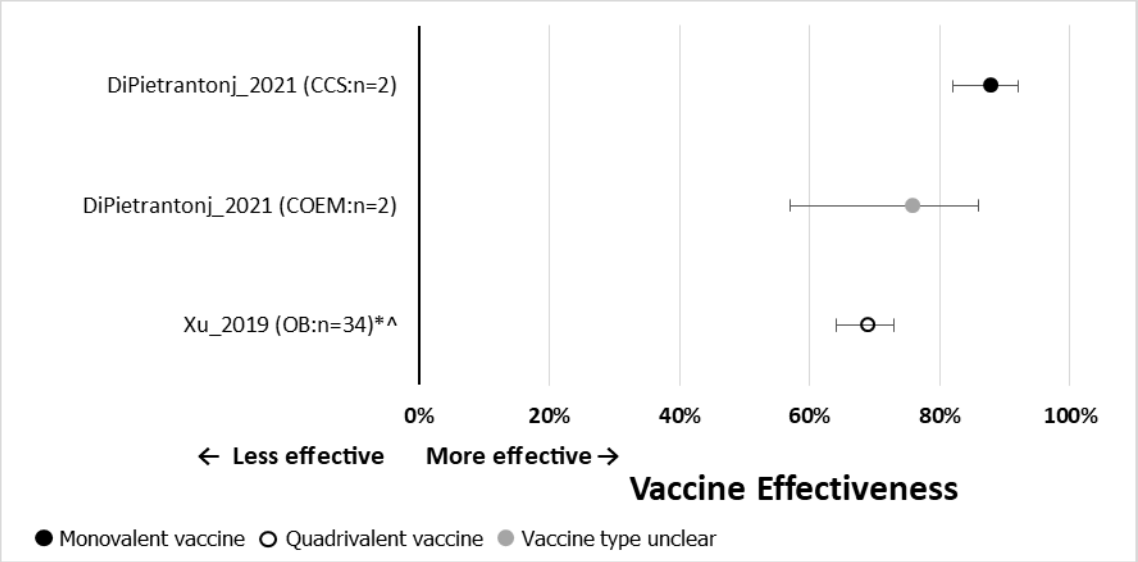
A single review reported pooled vaccine effectiveness of any-dose of quadrivalent vaccine against varicella of 76% (95% CI: 57 to 86%; $I^2$=100%; 2 case-only ecological method studies).[91] The same review reported vaccine effectiveness of any-dose of the quadrivalent vaccine (Priorix-Tetra®) of 86% (95% CI: 72 to 93%; 1 case-control study) against varicella of any severity and 93% (95% CI: 83 to 97%; 1 case-control study) against moderate or severe varicella.[91]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

A total of three reviews reporting on vaccine efficacy and effectiveness did not specifically state the dosing schedule and the vaccine type used.[95, 101, 107] A meta-analysis conducted in outbreak settings in China only reported vaccine effectiveness of any-dose in preventing varicella of 69% (95% CI: 64 to 73%, $I^2$=69%; 34 studies).[101] In this review, vaccine effectiveness was significantly lower between pre-school (78% [95% CI: 60 to 87%, $I^2$=0%, 2 estimates]) and primary school settings (33% [95% CI: 4 to 54%, $I^2$=0%, 3 estimates]) ($p<0.00001$).[101] In the same review, against a backdrop of a vaccination recommendation from 12 months old, vaccine effectiveness was estimated to reduce by age, from 94% (95% CI: 69 to 99%, $I^2$=91%; 3 estimates) for those aged <5 years old to 41% (95% CI: 23 to 54%, $I^2$=0%; 5 estimates) for those aged ≥9 years old.[101] In a second review that included a narrative synthesis of findings, vaccine efficacy or effectiveness against varicella of any severity was reported at ≥80% and between 97% and 100% against moderate or severe varicella (data from three systematic reviews, an RCT and three other studies).[95] A further narrative review reported vaccine effectiveness of 88% for varicella of any severity and 100% for moderate or severe varicella (from one case-control study) in the first three years after vaccination introduction.[107] In outbreak settings, vaccine effectiveness against varicella of any severity was reported at 81% in one review (1 retrospective cohort study) and ranged from 20 to 93% (data from three systematic reviews, one meta-analysis and five other studies) in another review.[95]

Figure 4.3.4 provides a summary of estimates of pooled any-dose vaccine effectiveness from reviews that conducted a meta-analysis. Study type, number of primary studies, follow-up period (if provided) and vaccine type are detailed for each review.

**Figure 4.4 Pooled vaccine effectiveness (95% confidence interval) of any-dose varicella vaccination in preventing varicella of any severity (by review and study type)**




Comparator: The comparator for all estimates was no vaccination
*Review includes studies from China only
^Outbreak setting only
**Key:** CCS – case-control study; COEM – case only ecological method study; OB – observational study (study type not clear);

#### 4.3.2.4.2 Impact on incidence of varicella

**Monovalent or quadrivalent vaccine (vaccine type not clear)**

In one narrative review, where dosing schedule and vaccine type were not clear, it was reported that nine observational studies (no further detail provided) demonstrated that incidence of varicella decreased by 34 to 90% over a period of four to 10 years (nine studies) following the introduction of routine varicella vaccination.[95] A second narrative review reported findings from observational studies from Sicily demonstrating significant reductions in incidence of varicella in all age groups over a three year period following introduction of the vaccine, but significant reductions in incidence of varicella in the 1 to 4 year old age group only in Brazil.[107]

#### 4.3.2.4.3 Impact on hospitalisation and complications associated with varicella

**Quadrivalent MMRV vaccine**

A pooled analysis of data from three case only ecological method studies reported vaccine effectiveness of 57% (95% CI: 45 to 66%; $I^2$=60%; 7 estimates) in reducing hospitalisations associated with varicella.[91]

**Monovalent or quadrivalent vaccine (vaccine type not clear)**

In one narrative review, hospitalisations associated with varicella were reported to have declined by 43 - 88% for all age groups over a period of five to 15 years after vaccination introduction (eight studies), and complications associated with varicella were reported to have decreased (four studies).[95] A second review highlighted findings from a retrospective study in the US showing decreases in hospitalisation rates when the pre- and post-UVV periods were compared, although showing no significant difference in the mean age or length of stay of hospitalised patients.[107]

#### 4.3.2.4.4 Incidence of and risk factors for breakthrough varicella (BV)

In one region of Italy, where two-dose UVV was introduced in 2009, it was reported that BV decreased from 40.5% of cases of varicella infection in the first vaccinated cohort to 4.5% in the third vaccinated cohort (1 surveillance study).[36] The observed differences could be accounted for in changes in coverage rates and or dosing. A single review reported on risk factors for BV, but was not specific regarding dosing schedule or vaccine type.[95] It reported that younger age at vaccination (≤14 to 18 months) may be a risk factor, although the evidence was inconsistent. However, children vaccinated at an age of ≤2 years may be at lower risk for moderate or severe BV compared with children vaccinated at an older age.[95] The review also reported that evidence indicates that if BV occurs, moderate or severe cases are more often observed with increasing time since immunisation.[95] Lastly, the review reported a single study that showed that varicella vaccine administration within 28 days of receipt of the measles, mumps rubella (MMR) vaccine increased the risk for BV.[95]

### 4.3.3 Quality Appraisal

Quality appraisal was conducted independently by two reviewers using AMSTAR 2.[87] The majority of reviews had multiple methodological flaws with one review deemed 'high' quality,[91] one review deemed 'low' quality[36] and 18 reviews deemed 'critically low' quality.[90, 92-108] None of the 'critically low' quality reviews included a protocol or explicit statement that the review methods were established prior to the conduct of the review. The search strategies were not considered comprehensive in

the 'critically low' quality reviews, lacking searches of reference lists and grey literature, not providing justification for foreign language exclusions, not providing clear dates for searches or not publishing within two years of the search end date. A list of excluded studies and reasons for exclusions were provided for two reviews only.[36, 91] Included studies were fully described in adequate detail in three reviews only.[91, 103] A total of 13 reviews either did not conduct a risk of bias assessment of individual studies included in the review or where it was indicated that it was conducted, the tool used was not clear and results were not provided.[94-98, 101-108] In seven of the ten reviews that included a meta-analysis, it was not clear if estimates had been adjusted.[90, 93, 96, 98-101] The full set of results for the quality appraisal are provided in the supplementary file (Appendix A4.3).

### 4.3.4 Overlap within included reviews

Overlap calculations were calculated based on 18 of the 20 included reviews as primary publications were not identifiable in two reviews.[99, 101] A total of 318 primary publications were identified, with 221 index publications (primary publications that are counted on their first occurrence only).[89] The total of 221 index publications included 15 RCTs and 206 other primary studies/reviews. Three RCTs were included in more than one review and 94 other studies/reviews were included in more than one review. The overall corrected covered area was calculated at 2.58, indicating slight overlap among index publications.[89]

## 4.4 Discussion

Overall, 20 systematic reviews that assessed the efficacy/effectiveness and impact of varicella vaccination were included in this overview of reviews. While the majority of reviews contained multiple methodological flaws and only one review was deemed 'high' quality,[91] it is noted that that there is substantial evidence underpinning the efficacy/effectiveness of varicella vaccination, comprising 15 RCTs and 206 other primary studies/reviews. These data describe a range of vaccination strategies; monovalent and quadrivalent, one- and two-dose, with differing age at first vaccination, differing intervals between doses, across non-specific settings as well as clusters/outbreaks, and where administered as part of UVV, with differing rates of vaccination coverage.

### 4.4.1 Efficacy / effectiveness in preventing varicella

Based on meta-analyses conducted within seven reviews, the efficacy/effectiveness of one-dose vaccination strategies (both monovalent and quadrivalent varicella vaccine types) against varicella of any severity ranged from 67% efficacy (monovalent vaccine) up to 10 years after vaccination,[91] to 88% effectiveness (vaccine type and follow-up not reported).[100] In outbreak settings specifically, one-

dose effectiveness ranged from 54% (vaccine type not reported) nine to 10 years after vaccination to 73% (vaccine type and follow-up not reported).[98] Findings from reviews that provided a narrative synthesis of the effectiveness of one-dose varicella vaccination support these estimates, including those of Kaufmann et al.,[36] reporting the experience from Germany, Arlant et al.,[103] reporting the experience from Brazil and two additional general systematic reviews.[106, 107] The evidence also suggests that one-dose vaccination strategies are highly effective against more severe disease (that is, moderate to severe varicella) with effectiveness estimates ranging from 90 to 100%.[91, 97, 106, 107]

Based on meta-analyses, the effectiveness of two-dose varicella vaccination strategies to prevent varicella of any severity ranged from 87% (quadrivalent) to 95% (monovalent vaccine).[91] In outbreak settings specifically, two-dose effectiveness ranged from 87% (vaccine type not reported)[90] to 92% (vaccine type not reported).[101] These estimates were supported by findings in additional reviews that reported two-dose vaccine effectiveness in excess of 90% against varicella of any severity.[36, 106-108] The evidence on the efficacy/effectiveness of two-dose vaccination in preventing moderate and severe varicella was limited to a single review reporting 99% efficacy for two-dose quadrivalent MMRV vaccination at 10 year follow-up post vaccination.[91]

Across all reviews, conclusions were consistent that one- and two-dose varicella vaccination strategies are effective in preventing varicella of any severity with greater protection seen against severe disease (moderate and severe varicella). Additionally, two-dose vaccination appears to be more effective than one-dose in preventing varicella of any severity, a finding that is supported by a number of reviews.[36, 92, 93, 97] While vaccine effectiveness appears to be lower in outbreak settings for one-dose strategies, possibly due to a higher force of infection, this does not appear to be the case for two-dose strategies. Although the direction of effect is consistent across reviews, given the 'critically low' quality assigned to the majority of systematic reviews, the magnitude of effect for both dosing schedules is uncertain.

### 4.4.2 Waning immunity

A number of reviews reported evidence of waning immunity following vaccination. In many of the reviews, the age at which children were vaccinated was unclear, with outcomes reported as incidence of infection by age; a number of reviews reported incidence according to the number of years post vaccination. Evidence of waning immunity differed between one-dose and two-dose strategies and while waning occurred, most notably against varicella of any severity for a one-dose strategy, there was still evidence of protection up to 10 years post vaccination.

With respect to one-dose vaccination strategies, two reviews limited to populations in China only, reported a lower vaccine effectiveness in older children, ranging from 84% in those aged <6 years old to 60% in those aged ≥6 years old[99] and from 90% in pre-school children to 67% in children attending primary school.[100] A third review in clusters/outbreaks only, reported vaccine effectiveness of 70% six to eight years post-vaccination and 54% nine to ten years post-vaccination.[101] These findings of waning immunity with one-dose vaccination strategies are consistent with findings from a number of additional reviews including the only review deemed 'high' quality, where vaccine efficacy was estimated at 67% up to 10 years post vaccination.[91] The evidence on the effectiveness of two-dose vaccination over time was limited to two reviews, but suggests less waning of immunity compared with one-dose strategies. Estimates ranged from 95% efficacy at 10 years post vaccination follow-up [91] to 98.3% effectiveness over an observational period of up to 10 years post vaccination.[107] Evidence of waning immunity was also reported against a backdrop of a vaccination recommendation from 12 months old, where vaccine effectiveness in outbreak settings (vaccine type and dose unclear) was estimated to reduce by age, from 94% for those aged less than five years to 41% for those aged nine years or older.[101]

With respect to moderate or severe varicella specifically, the evidence suggests that there is little waning of immunity up to 10 years post vaccination; high levels of protection were reported for both one- (90% efficacy) and two-dose (99% efficacy) strategies.[91] Efficacy of 95% was reported for a one-dose strategy against severe varicella at between five and 10 years follow-up post vaccination.

### 4.4.3 Impact on incidence of varicella

The impact of varicella vaccination programmes on population-level incidence of varicella was limited to a number of narrative reviews reporting results largely from surveillance studies. These mostly related to the introduction of one-dose varicella vaccination strategies as part of childhood immunisation programmes. Most reviews reported reduced incidence of varicella following the introduction of vaccination, including in Costa Rica (up to 79% in those <5 years old)[103], Germany (63 to 75% in those <4 years old),[36] Abu Dhabi,[102] Sicily,[107] Saudi Arabia,[102] Taiwan[104] and regions of Brazil.[103, 107] However, in both Australia and South Korea, higher incidence of varicella was reported following the introduction of one-dose vaccination programmes, possibly explained by under reporting prior to the implementation of the vaccination programme and the impact of the introduction of varicella notification (rather than an increase in disease), respectively.[104] In countries (a number of Italian regions and in Germany) that switched from one-dose to two-dose vaccination programmes, further decreases in incidence of varicella were reported following the switch.[36]

### 4.4.4 Impact on complications and hospitalisation associated with varicella

There was evidence from a number of countries, including Australia,[104, 106] Costa Rica,[103] Germany[36, 106] Uruguay,[103] USA,[106] and a number of regions in Italy,[36] of reductions in varicella-related hospitalisations following the introduction of one-dose vaccination. These findings were supported by a pooled analysis reporting vaccine effectiveness (quadrivalent vaccine) of 57% in reducing hospitalisation associated with varicella, with estimates greatest (71%) for children aged one to four years.[91] Further reductions in hospitalisation associated with varicella were reported for a number of regions in Italy and in Germany following the introduction of two-dose UVV, with regions in Germany with the highest vaccination coverage observing the highest declines.[36]

There was also evidence of decreases in complications associated with varicella in Costa Rica,[103] Germany,[36] Italy[36] and Uruguay[103] following the introduction of one-dose UVV. In Puerto Rico there was evidence of decreases in morbidity associated with varicella, following the move from a one- to a two-dose strategy.[103]

The impact on mortality associated with varicella was less clear, possibly due to the rarity of this event. In Costa Rica, no difference in mortality was reported when the pre- and post- one-dose UVV eras were compared[103] while a decrease was reported in the US[95] and evidence in Taiwan was conflicting.[104]

### 4.4.5 Breakthrough varicella

The evidence on incidence of breakthrough varicella is consistent with the evidence on vaccine effectiveness rates for one- and two-dose vaccination strategies over time. Higher risk[107] and higher incidence rates of BV were reported for one-dose compared with two-dose strategies up to at least 10 years post vaccination, with higher incidence rates eight years after vaccination compared with the first year after vaccination.[93]

### 4.4.6 Strengths and Limitations

The main strength of this overview of reviews is that it provides a comprehensive synthesis of the published and unpublished evidence on the effectiveness of varicella vaccination since the development of the varicella vaccine in the 1970s. The overview captures changes in vaccine development and varying programmes of administration, including differing dosing schedules, over time. The overview search involved a comprehensive electronic database and grey search and was conducted without date and language restriction to ensure that all possible relevant reviews

were identified; it includes five non-English publications, one publication in Portuguese and four in Chinese. The evidence from the included reviews originates from many regions and countries across the globe, ensuring that the results are broadly generalisable.

However, there are a number of important limitations. Firstly, the quality of the reviews included in this overview was largely deemed 'critically low'. With the exception of one review, all reviews had methodological flaws which lowers the certainty of the evidence. However, it is noted that although the quality of reviews was largely assessed as 'critically low', the overall quality of the underpinning primary studies (15 RCTs and 206 other primary studies/reviews) could not be ascertained as risk of bias assessments were not conducted for many reviews. Secondly, the source of evidence in 13 of the systematic reviews was solely observational, raising potential issues with bias and confounding. Lastly, of the ten reviews that included a meta-analysis, five were limited to studies conducted in China.

In assessing the potential introduction of an immunisation programme for a disease such as varicella that has a high reproduction number, possible vaccination uptake and the impact of uptake on programme effectiveness is an important consideration. However, the reviews that examined the impact of UVV either regionally or countrywide reported limited data on vaccination coverage rates; where they were reported, they didn't necessarily correspond with the timeline of reported programme outcomes. Varied vaccination coverage data in individual studies was also reported in one included review and was highlighted as an area that requires further research.[102] The lack of vaccination coverage data alongside corresponding outcome data limits the interpretation and understanding of the full impact of existing UVV programmes.

There were also a number of issues that hampered the comparison between reviews and the synthesis across reviews. For both types of reviews, that is those that included a meta-analysis and those that included a narrative summary of findings only, the reporting of some of the systematic reviews lacked critical detail. This included lack of detail on vaccine type administered, dosing-schedule, age at vaccination, and follow-up period after vaccination. Additionally, there were a number of evidence gaps in the literature including limited evidence from the reviews on the effectiveness of two-dose quadrivalent vaccination against moderate/severe varicella, on vaccine effectiveness based on age at vaccination and on vaccine effectiveness based on interval between doses. From a policy perspective, the lack of detailed reporting and evidence gaps impact on the ability to fully inform policy decisions where the introduction of universal varicella vaccination

is being considered or where existing universal varicella vaccination programmes are under review.

### 4.4.8 Conclusion

The aim of this overview of reviews was to establish the clinical efficacy and effectiveness of potential varicella vaccination strategies by synthesising the evidence available from relevant systematic reviews that have been published to date. The quality of reviews eligible for inclusion in this review, as distinct from the studies included in those reviews, was deemed to be 'critically low'. Overall, however, there is clear and consistent evidence that vaccination is very effective at reducing varicella. While the analysis was restricted due to lack of detail in reporting of the systematic reviews, the evidence suggests that two-dose strategies are more efficacious/effective than one-dose strategies in preventing varicella of any severity, but that one- and two-dose strategies have similar high efficacy/effectiveness in preventing moderate or severe varicella. The evidence also suggests that one-dose strategies may be less effective in outbreak settings, but this may not be the case for two-dose strategies. Additionally, although evidence was limited with respect to two-dose strategies, there appears to be greater waning of immunity following one-dose than two-dose schedules.

# 5 Overview of reviews of the safety of potential varicella vaccination strategies

## Key points

- A number of systematic reviews assessing the safety of varicella vaccination have been published over the last 40 years. Early reviews assessed the monovalent vaccine and one-dose, while more recent reviews assessed both the monovalent and quadrivalent MMRV vaccines and one- and two-doses.
- The aim of this overview of reviews was to establish the clinical safety of potential varicella vaccination strategies by synthesising the evidence available from relevant systematic reviews that have been published to date.
- In total, 17 systematic reviews were included in the overview of reviews; six assessed the safety of one-dose varicella vaccination, 4 assessed the safety of two-dose vaccination, 2 assessed two- versus one-dose vaccination and 14 reviews did not specify the number of vaccine doses.
- While the analysis by vaccine type and dosing strategy was restricted due to lack of detail in reporting of the systematic reviews, overall, there was clear and consistent evidence from a substantial evidence base, comprising 34 RCTs and 62 other primary studies/reviews, that that both monovalent and quadrivalent varicella vaccination are safe.
- The evidence suggests that mild local and systemic reactions, such as fever and rash, are relatively common, and while febrile seizures are possible adverse effects of both the monovalent and quadrivalent MMRV vaccine, serious adverse events are rare.
- The limited evidence on the co-administration of the varicella vaccine with other vaccines suggests that co-administration does not compromise the safety of the vaccines.
- The potential harms associated with varicella vaccination must be considered in light of the clinical benefits associated with reduced rates of varicella zoster virus infection and incidence of varicella disease.

## 5.1 Introduction

The aim of this chapter is to review the safety of potential varicella vaccination strategies.

## 5.2 Methods

A number of systematic reviews assessing the safety of varicella vaccines have been published over the last 40 years, with early reviews based on the monovalent vaccine and a one-dose schedule, while more recent reviews are based on both the monovalent and quadrivalent MMRV vaccines and one- and two-dose schedules. The number and variety of systematic reviews reflect the evolution of varicella vaccination strategies since the development of the vaccine in the 1970s and the varying vaccination strategies currently evident between countries. However, no single existing systematic review captures the range of possible vaccination strategies across multiple safety outcomes. Therefore, in order to assess the safety of potential varicella vaccination strategies at this point in time, an overview of reviews was undertaken to produce a comprehensive and comprehensible summary of the relevant evidence generated since the development of the first live attenuated monovalent varicella vaccine almost 50 years ago.[80]

Many of the methods used to conduct a systematic review were applied to this overview of reviews. While guidance for conducting an overview of reviews continues to accumulate, recently published methodological guidance, Chapter V of Part I of the Cochrane Handbook for Systematic Reviews and Chapter 10 of the Joanna Briggs Institute's Manual for Evidence Synthesis, was used in the design and conduct of this review.[81-83]

### 5.2.1 Review protocol

This overview of reviews was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[84]and the protocol was registered with the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42022312325.

### 5.2.2 Research question

The specific question for this overview of reviews was developed to reflect the safety outcomes associated with varicella vaccination. The PICO (Population, Intervention, Comparator, Outcomes) framework used to formulate the research question is presented in Table 5.1.

## Table 5.1 Review inclusion and exclusion criteria

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

### 5.2.3 Search strategy

The search was conducted as part of a broader search for reviews on the clinical effectiveness and safety of varicella vaccination strategies. A comprehensive electronic search was performed in Embase (Elsevier), Medline (EBSCO), the Cochrane Library and Google Scholar on 2 February 2022, with databases searched since inception. The SYSVAC and PROSPERO registries were also searched to identify relevant reviews and registered protocols for forthcoming systematic reviews. These searches were supplemented by a grey literature search of the Trip medical database, and the International Health Technology Assessment (HTA) database. Websites of health technology assessment (HTA) agencies and government health

ministries from the countries ranked 1-50 in the Human Development Index,[85] and websites of a number of international health agencies, were searched. A full list of website domain names that were searched is provided in the supplementary file (Appendix A5.1). A non-domain specific Google search was also conducted. All search strings, developed in consultation with an information specialist, dates of searches and search results are provided in the supplementary file (Appendix A5.1). The references lists of included reviews were searched and forward citation searches of included reviews were conducted to identify additional relevant reviews. No date or language restrictions were applied.

### 5.2.4 Review selection, data extraction and management

Titles and abstracts of potentially eligible reviews were screened independently by two reviewers using Covidence software.[86] Full text reviews were independently assessed for eligibility by two reviewers according to the pre-specified inclusion and exclusion criteria outlined in Table 5.2. Any disagreements with screening or uncertain inclusions were resolved through discussion and with third party arbitration when required. Data extraction for each review was conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements in screening, eligibility and data extraction were resolved through discussion and with third party arbitration when required.

### 5.2.5 Assessment of the methodological quality of included reviews

Two reviewers independently assessed the quality of each review using the AMSTAR 2 tool, "A MeaSurement Tool to Assess systematic Reviews, version 2".[87] Disagreements were resolved by discussion and with third party arbitration when required.

### 5.2.6 Data synthesis

Summary characteristics of included reviews and overall findings are presented in table format by safety outcome measure. As this is an overview of reviews, findings that were extracted from the included reviews are synthesised narratively by dosing schedule, outcome and vaccine type, that is monovalent, quadrivalent MMRV, and monovalent or quadrivalent (where the vaccine type was not specifically reported). Given that the Preferred Reporting Items for Overviews of Reviews (PRIOR)[88] guidelines have not yet been published, the reporting of this overview adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.[84]

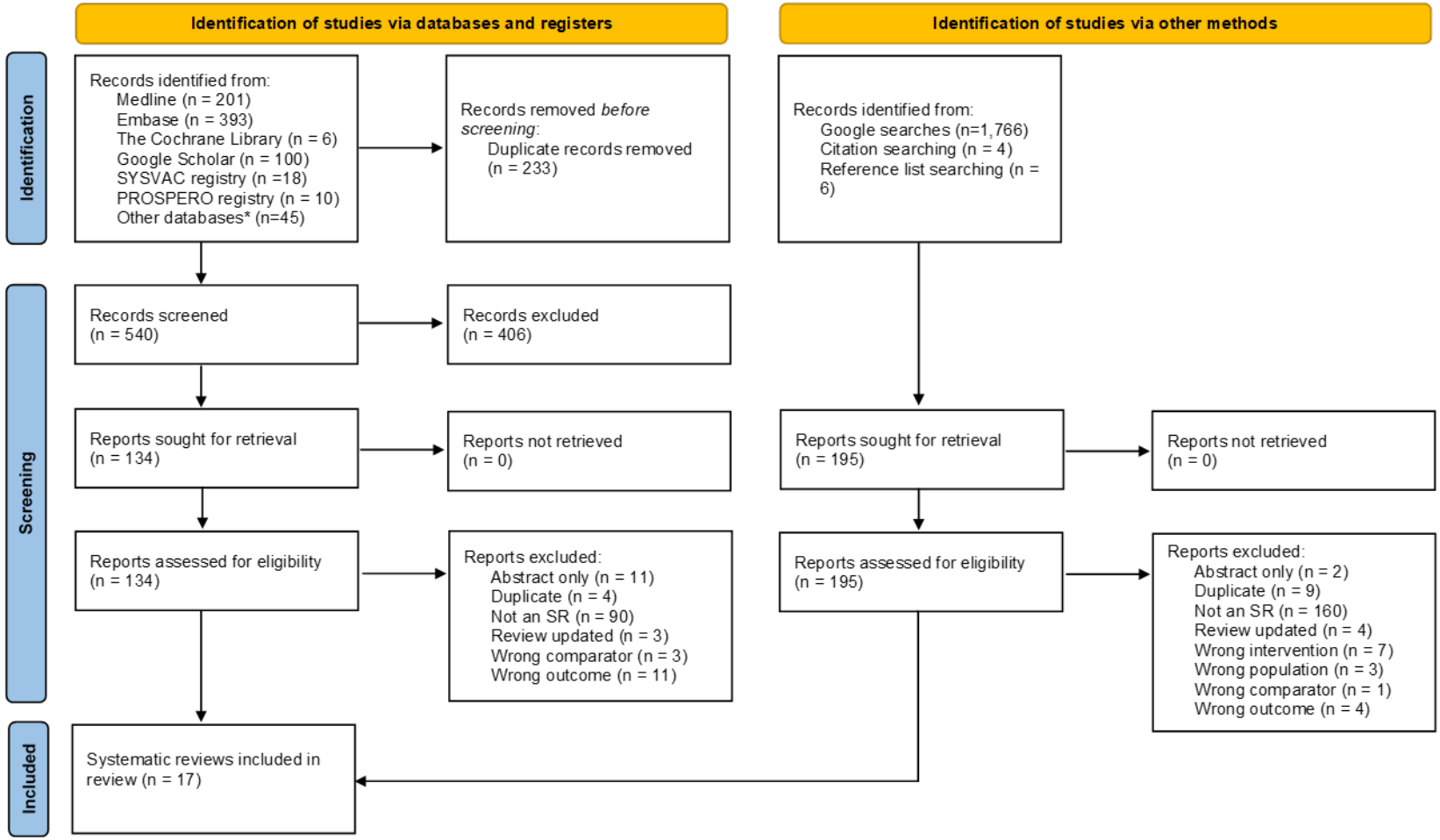
### 5.2.7 Overlap within included reviews

Overlaps of original research studies in each of the included reviews were identified where possible. The level of overlap was determined by calculating the corrected covered area, a measure of overlap calculated by dividing the frequency of repeat occurrences of the index publication in other reviews by the product of index publications and reviews, reduced by the number of index publications.[89] A corrected cover area of 0-5 indicates slight overlap, 6-10 moderate overlap, 11-15 high overlap and >15 very high overlap [89]

## 5.3 Results

After removing duplicates, the initial search identified a total of 540 articles from databases and registers (n=497 articles) and grey literature sources (n= 43 articles). A total of 1,766 articles were identified from the initial Google domain- and non-domain specific searches. After excluding articles based on title and abstract review, a total of 316 articles (on clinical effectiveness and safety) remained for full text review (n=131 from databases, registers and grey literature sources and n=185 from Google). Following full text review and subsequent exclusion, 13 systematic reviews related to safety remained for inclusion in this overview of reviews (n=12 from databases, registers and grey literature sources and n=1 from google). An additional four eligible reviews were identified from reference checking (n=2) and forward citation searching (n=2) of included reviews, giving a final total of 17 eligible systematic reviews (Figure 5.1).

## Figure 5.1 PRISMA 2020 flow diagram of review selection




*TRIP database and International Health Technology Assessment database
Key: SR – systematic review;

### 5.3.1 Characteristics of included reviews

In total, 17 systematic reviews were identified that met the inclusion criteria for the safety of varicella vaccination. The most recent specified end search date within the reviews was November 2020.[109] Of the 17 reviews, one review included RCTs only,[110] six reviews included RCTs and observational studies[94, 107-109, 111, 112] of which one also included two previously published systematic reviews,[107] two included RCTs and other study types that were unclear,[95, 106] five included observational studies only, [91, 92, 113-115] two included case reports only[116, 117] and the study types were not clear in one review.[118] Of the two systematic reviews that were themselves included in an eligible systematic review for this overview,[107] neither met the pre-defined eligibility criteria for a systematic review and were therefore not included in this overview; one included a search of one database only and search terms were not provided in the other.

Four of the 17 reviews that assessed safety provided a meta-analysis,[91, 92, 110, 112] two of which included a meta-analysis of RCT data[110, 112] The remaining thirteen reviews provided a narrative summary of findings.[94, 95, 106-109, 111, 113-118] None of the 17 reviews had a geographic limitation. Completed data extraction tables for all included reviews are provided in the supplementary file (Appendix A5.2).

### 5.3.2 Safety of varicella vaccination

For ease of reading, the evidence in relation to the safety of varicella vaccination is presented in a number of separate sections. A narrative synthesis of the findings of this overview of reviews is presented by safety outcome, vaccine dose and vaccine type, that is monovalent, quadrivalent MMRV, and monovalent or quadrivalent (where the vaccine type was not clearly specified in the review). Tables 5.2 and 5.3 provide an overview of the characteristics of included systematic reviews by safety outcome.

The 17 reviews that examined the safety of varicella vaccination included the following dosing strategies:

- one review included one-dose only[94, 96, 98-100, 104, 105, 113]
- five reviews included three or more (of one-, two-, two- versus one- or any-dose) different dosing schedules[94, 95, 106, 110, 112]
- one review included two- versus one-dose only[92]
- ten reviews included any-dose (at least one-dose) only.[91, 107-109, 111, 114-118]

## Table 5.2 Overview of included systematic reviews on varicella vaccination by safety outcome (general)

| Outcome | Review | Dose | Type of vaccine | Type of studies | Type of analysis | Date of last search |
|---|---|---|---|---|---|---|
| Tolerance | NZ_2012[106] | 2-dose | Quadrivalent | RCT | NS | Nov 2011 |
| | Ma_2015a[110] | 2-dose | Quadrivalent | RCT | NS | Sep 2014 |
| | NZ_2012[106] | Any-dose | Quadrivalent | RCT | NS | Nov 2011 |
| | NZ_2012[106] | Any-dose | Unclear | Unclear | NS | Nov 2011 |
| Reactions | Skull_2001[94] | 2- v 1-dose | Unclear | Unclear | NS | Dec 2000 |
| Local adverse events (pain, redness, swelling) | Pallas_2011[95] | 1-dose | Monovalent and quadrivalent | RCT and feasibility | NS | Unclear (2010/2011) |
| | Ma_2015a[110] | 1-dose | Quadrivalent | RCT | NS | Sep 2014 |
| | Yin_2018[92] | 2- v 1-dose | Quadrivalent | Self-controlled | MA | Jun 2017 |
| | Ma_2015a[110] | 2- v 1-dose | Quadrivalent | RCT | NS | Sep 2014 |
| | Skull_2001[94] | Any-dose | Unclear | RCT and others | NS | Dec 2000 |
| | NZ_2012[106] | Any-dose | Unclear | Unclear | NS | Nov 2011 |
| | Garrido_2012[107] | Any-dose | Unclear | RCT | NS | Nov 2009 |
| Systemic adverse events (fever, rash) | Pallas_2011[95] | 1-dose | Monovalent | RCT | NS | Unclear (2010/2011) |
| | Ma_2015a[110] | 1-dose | Quadrivalent | RCT | NS | Sep 2014 |
| | Pallas_2011[95] | 2-dose | Monovalent and quadrivalent | RCTs and review | NS | Unclear (2010/2011) |
| | Yin_2018[92] | 2- v 1-dose | Monovalent and quadrivalent | Self-controlled | MA | Jun 2017 |
| | Pallas_2011[95] | 2- v 1-dose | Quadrivalent | RCT | NS | Unclear (2010/2011) |
| | Bauwens_2019[111] | Any-dose | Monovalent co-administered with other vaccines | RCT | NS | Jan 2019 |
| | Skull_2001[94] | Any-dose | Unclear | RCT | NS | Dec 2000 |
| | Pallas_2011[95] | Any-dose | Unclear | RCT | NS | Unclear (2010/2011) |
| | NZ_2012[106] | Any-dose | Unclear | Unclear | NS | Nov 2011 |
| | Garrido_2012[107] | Any-dose | Unclear | RCT | NS | Nov 2009 |
| Adverse events | Pallas_2011[95] | 1-dose | Monovalent | RCT | NS | Unclear (2010/2011) |
| | Ma_2015a[110] | 1-dose | Quadrivalent | RCT | NS | Sep 2014 |
| | Garrido_2012[107] | 1-dose | Unclear | SR | NS | Nov 2009 |
| | Pallas_2011[95] | 2- v 1-dose | Quadrivalent | RCT | NS | Unclear (2010/2011) |
| | Bauwens_2019[111] | Any-dose | Monovalent co-administered with other vaccines | RCT | NS | Jan 2019 |
| | Bauwens_2019[111] | Any-dose | Quadrivalent co-administered with other vaccines | RCT | NS | Jan 2019 |
| | NZ_2012[106] | Any-dose | Quadrivalent co-administered with other vaccines | Unclear | NS | Nov 2011 |
| | Benchimol_2011[108] | Any-dose | Unclear | RCT, observational and post-licensure | NS | Apr 2019 |
| | Skull_2001[94] | Any-dose | Unclear | RCT and post-licensure | NS | Dec 2000 |
| Unsolicited adverse event - pharyngitis | Ma_2015a[110] | 1-dose | Quadrivalent | SR | NS | Sep 2014 |
| Seizure including febrile seizure | Ma_2015b[112] | 1-dose | Quadrivalent | RCT | MA | Dec 2014 |

| Outcome | Review | Dose | Type of vaccine | Type of studies | Type of analysis | Date of last search |
|---|---|---|---|---|---|---|
| | Ma_2015a[110] | 1-dose | Quadrivalent | RCT | NS | Sep 2014 |
| | Ma_2015b[112] | 2-dose | Quadrivalent | RCT | MA | Dec 2014 |
| | Ma_2015b[112] | 2-dose | Quadrivalent co-administered with other vaccines | RCT | MA | Dec 2014 |
| | DiPietrantonj_2021[91] | Any-dose | Monovalent and quadrivalent | SCCS/PTCS | MA | May 2019 |
| | VandenBoogaard_2021[117] | Any-dose | Quadrivalent | Case report | NS | Nov 2011 |
| | Gidengil_2021[109] | Any-dose | Monovalent and quadrivalent | Unclear | NS | Nov 2020 |
| | Ma_2015b[112] | Any-dose | Quadrivalent | Cohort & matched cohort | MA | Dec 2014 |
| | Gidengil_2021[109] | Any-dose | Quadrivalent | Unclear | NS | Nov 2020 |
| | NZ_2012[106] | Any-dose | Quadrivalent | Unclear | NS | Nov 2011 |
| Death | Ma_2015a[110] | 1-dose | Quadrivalent | SR | NS | Sep 2014 |
| | Skull_2001[94] | 1-dose | Unclear | RCT and post-licensure | NS | Dec 2000 |
| | Gidengil_2021[109] | Any-dose | Quadrivalent | Unclear | NS | Nov 2020 |
| | NZ_2012[106] | Any-dose | Unclear | Unclear | NS | Nov 2011 |
| | Garrido_2012[107] | Any-dose | Unclear | Observational | NS | Nov 2009 |

## Table 5.3 Overview of included systematic reviews on varicella vaccination by specific adverse event

| Outcome | Review | Dose | Type of vaccine | Type of studies | Type of analysis | Last date of search |
|---|---|---|---|---|---|---|
| Acute disseminated encephalomyelitis | Gidengil_2021[109] | Any-dose | Monovalent and quadrivalent | Unclear | NS | Nov 2020 |
| Anaphylaxis/systemic allergic reaction | Gidengil_2021[109] | Any-dose | Monovalent and quadrivalent | Unclear | NS | Nov 2020 |
| Arthritis or arthralgia | Panozzo_2019[114] | Any-dose | Unclear | Cohort | NS | Unclear (Dec 2017) |
| Arthropathy and cytopenia | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| Ataxia | Gidengil_2021[109] | Any-dose | Quadrivalent | Unclear | NS | Nov 2020 |
| Disseminated Oka VZV without other organ involvement | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| Gastroenteritis | Garrido_2012[107] | Any-dose | Unclear | RCT | NS | Nov 2009 |
| Guillain-Barre syndrome | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| Herpes zoster | NZ_2012[106] | 1-dose | Unclear | Various | NS | Nov 2011 |
| | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| | Skull_2001[94] | Any-dose | Unclear | RCT, cohort, surveillance | NS | Dec 2000 |
| Idiopathic thrombocytopenic purpura | VandenBoogaard_2021[117] | Any-dose | Monovalent | Case report | NS | Nov 2011 |
| | Gidengil_2021[109] | Any-dose | Quadrivalent | Unclear | NS | Nov 2020 |
| | DiPietrantonj_2021[91] | Any-dose | Quadrivalent | SCCS | MA | May 2019 |
| | Garrido_2012[107] | Any-dose | Unclear | RCT | NS | Nov 2009 |
| Kawasaki disease | Gidengil_2021[109] | Any-dose | Quadrivalent | Unclear | NS | Nov 2020 |
| | Phuong_2017[115] | Any-dose | Quadrivalent | Cohort | NS | Jun 2016 |
| Laryngospasm | Garrido_2012[107] | Any-dose | Unclear | RCT | NS | Nov 2009 |
| Meningitis | Gidengil_2021[109] | Any-dose | Quadrivalent | Unclear | NS | Nov 2020 |
| Pneumonia | Garrido_2012[107] | Any-dose | Unclear | RCT | NS | Nov 2009 |
| Sixth nerve palsy | VandenBoogaard_2021[117] | Any-dose | Monovalent | Case report | NS | Nov 2011 |
| Small fibre neuropathy | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| Stevens Johnson Syndrome | Grazina_2020[116] | Any-dose | Unclear | Case report | NS | Feb 2018 |
| Transverse myelitis | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis | Gidengil_2021[109] | Any-dose | Monovalent | Unclear | NS | Nov 2020 |
| Varicella reactivation meningitis | Amaral_2021[118] | Any-dose | Unclear | Case report | NS | Jun 2020 |
| Varicella transmission from vaccinated individuals | Skull_2001[94] | Any-dose | Unclear | RCT and case report | NS | Dec 2000 |
| vOka transmission | Marin_2019[113] | 1-dose | Unclear | NR | NS | Dec 2018 |

Key: MA - meta-analysis; NR - not reported; NS - narrative synthesis; PTCS - person time cohort study; RCT - randomised controlled trial; SCCS - self-controlled case series; SR - systematic review; vOka - vaccine strain varicella;

#### 5.3.2.1 One-dose varicella vaccination

A total of six reviews assessed the safety of one-dose varicella vaccination strategies,[94, 95, 106, 110, 112, 113] with two reviews providing a meta-analysis[110, 112] and four reviews providing a narrative synthesis of findings.[94, 95, 106, 113] The monovalent vaccine was assessed in one review,[95] the quadrivalent vaccine was assessed in three reviews,[95, 110, 112] and the vaccine type was not clear (that is, monovalent or quadrivalent) in three reviews.[94, 106, 113] One review assessed both monovalent and quadrivalent vaccines.[95] A narrative summary of results by safety outcome measure and vaccine type is provided below.

##### 5.3.2.1.1 Local adverse events (pain, redness, swelling)

**Monovalent vaccine**

Local adverse events from a number of RCTs and one feasibility study were reported in one review.[95] A higher incidence of injection-site adverse events at varicella vaccine injection sites than at measles mumps rubella (MMR)-injection sites were reported (2 RCTs).[95] Additionally, one RCT reported higher incidence of injection-site adverse events when separate MMR and varicella vaccines were given concomitantly rather than six weeks apart.[95] An additional two RCTs and one feasibility study reported that pain, redness and swelling were more frequent at varicella vaccine injection sites than at MMR-injection sites, with no differences observed between different monovalent varicella vaccine brands.[95]

**Quadrivalent MMRV vaccine**

In one review, no significant differences were reported in incidence of pain, redness or swelling, within four days after vaccination between those who received one-dose MMRV (Priorix-Tetra®) and those who received one-dose MMR. Similarly, the incidence of more severe (Grade 3+ level) reactions, which were rare (<0.5%) for both groups, did not differ between the MMRV and MMR groups (6 RCTs).[110] A further review reported no difference in the frequency of local adverse events between recipients of MMRV and MMR vaccines (2 RCTs).[95]

##### 5.3.2.1.2 Systemic adverse events (fever and rash)

**Monovalent vaccine**

A single review reported that incidences of fever and rash were not different between recipients of MMR+V and MMR (3 RCTs), with rashes reported very infrequently.[95] In the same review, a further two RCTs reported slightly higher incidence of fever in recipients of MMR+V than in recipients of MMR. [95] Lastly, the review reported results from an RCT where fever (any) occurred in 66.2% of

Australian children receiving MMR+V compared with 55.8% of those receiving MMR vaccine only, while rash occurred in 39% of all MMR+V recipients and in 29.9% of all MMR recipients.[95]

**Quadrivalent MMRV vaccine**

Irrespective of follow-up period (0-15 days or 0-42 days after vaccination), significantly higher incidences of fever (any) were reported in MMRV (Priorix-Tetra®) group than in the MMR group (pooled RRs ranged from 1.19 [95% CI: 1.13 to 1.25] to 1.60 [95% CI: 1.33 to 1.92]) after one-dose (1 systematic review (SR): 5 RCTs); pooled incidence of fever was reported to be approximately 60% in the MMRV group and 50% in the MMR group, the majority of which were reported during the first 15 days (days 0–14) after vaccination.[110] Incidence of varicella-like rash was significantly higher in MMRV (Priorix-Tetra®) groups than MMR groups (pooled RR 1.95, 95% CI: 1.04 to 3.66, $I^2$=0%, p=0.040; 1 SR: 3 RCTs) within 43 days after one-dose, with pooled incidence rates of 2.82% and 1.37% for the MMRV and MMR groups respectively.[110]

#### 5.3.2.1.3 Adverse events (including serious adverse events)

**Quadrivalent MMRV vaccine**

A single review reported that incidence of any serious adverse event after one-dose was approximately 1% in both MMRV and MMR groups (2 RCTs).[110]

#### 5.3.2.1.4 Febrile seizures

**Quadrivalent MMRV vaccine**

A meta-analysis reported no statistically significant difference in incidence of febrile seizures between MMRV and MMR vaccine recipients, either 0-42 days (pooled RR 0.71 (95% CI: 0.19 to 2.74; 4 RCTs) or 7-10 days after one-dose vaccination (pooled RR 0.51 (95% CI: 0.03 to 8.08; 2 RCTs).[112] Similarly, no statistically significant difference in incidence of vaccine-related febrile seizures between MMRV and MMR vaccine recipients was reported 0-42 days vaccination (pooled RR 1.39 (95% CI: 0.39 to 4.98; 5 RCTs) or 7-10 days after vaccination (pooled RR 1.39 (95% CI: 0.39 to 4.98; 5 RCTs).[112] A second review reported that the incidence of vaccine-related febrile seizure was <0.8% in MMRV groups and <0.5% in MMR groups, and that there was no statistical difference found between groups and no evidence of heterogeneity (5 RCTs).[110]

**Quadrivalent MMRV vaccine – co-administration with another vaccine**

A single review, that included a meta-analysis, reported no statistically significant difference in the incidence of febrile seizures or vaccine-related febrile seizures for the MMRV vaccine when co-administered with other vaccines compared with other vaccines alone (other vaccines not clear) either 0-28/42 days or 7-10 days after vaccination.[112]

#### 5.3.2.1.5 Unsolicited adverse events

**Quadrivalent MMRV**

In a single review examining 15 pre-specified unsolicited adverse events from three RCTs, incidence of pharyngitis was statistically higher in the MMRV (Priorix-Tetra®) group compared with the MMR group (pooled RR 1.37, 95% CI: 1.09 to 1.72, $I^2$ = 31%; p=0.008) within 43 days after one-dose.[110]

#### 5.3.2.1.6 Herpes zoster

**Quadrivalent MMRV**

A single review noted that at an individual study level, most studies suggest that the risk of herpes zoster following a single dose quadrivalent varicella vaccination is lower than the risk following wild-type varicella infection.[106]

#### 5.3.2.1.7 vOka (vaccine strain varicella) transmission from vaccine recipient

**Monovalent or quadrivalent vaccine (vaccine type not clear)**

A single review included 12 case reports of vOka transmission from varicella vaccine recipients.[113] A total of three confirmed cases of vOka transmission from a vaccine recipient with varicella-like rash were reported, with secondary cases developing a rash or lesions 16 to 19 days after rash onset in the index case.[113] Five confirmed cases of vOka transmission from a vaccine recipient (one confirmed MMRV) with herpes zoster were reported, with secondary cases developing a rash, lesions or fever within 14 to 19 days after herpes zoster onset in the index case.[113] A further four unconfirmed cases of vOka transmission were reported, with secondary cases developing varicella or a rash between six and 40 days after index cases were vaccinated.[113] The review concluded that the risk of healthy, vaccinated people transmitting vOka to contacts is minimal and only if a rash is present, with resulting secondary cases of varicella typically mild.[113]

#### 5.3.2.1.8 Death

**Quadrivalent MMRV vaccine**

A single review reported that no related fatal SAE was reported in any studies (5 RCTs) in the review.[110]

**Monovalent or quadrivalent vaccine (vaccine type not clear)**

An early review (2001) providing a narrative synthesis noted that no deaths have been reported for subjects in either vaccine or placebo groups for controlled varicella vaccine trials. The same review also reports of a post-licensure study that found 14 deaths temporally related to 9.7 million doses of varicella vaccine; of the five presented case reports, none had proven vaccine strain VZV.[94]

### 5.3.2.2 Two-dose varicella vaccination

A total of four reviews assessed the safety of two-dose varicella vaccination,[95, 106, 110, 112] with two reviews providing a meta-analysis[110, 112] and two reviews providing a narrative synthesis of findings.[95, 106] The monovalent vaccine was assessed in one review,[95] and the quadrivalent vaccine was assessed in three reviews.[106, 110, 112] One review assessed both monovalent and quadrivalent vaccines.[95] A narrative summary of the results by safety outcome measure and vaccine type is provided below.

#### 5.3.2.2.1 Tolerance

**Quadrivalent MMRV vaccine**

A single review noted that two-dose quadrivalent MMRV administered in the second year of life was well tolerated whether administered with a dose interval of four weeks or 12 months (1 RCT).[106] A second review reported MMRV was well tolerated when given as a second dose after MMR (3 RCTs) or MMR+V (2 RCTs) vaccination in children aged 15 months to 6 years.[110]

#### 5.3.2.2.2 Adverse events (including serious adverse events)

**Monovalent vaccine**

The results of an RCT were reported in one review where the proportion of children experiencing at least one adverse event after the second dose was similar between recipients of MMR and varicella vaccine MMR+V (75.6%) and MMR alone (78.0%), with no vaccine-related serious adverse experiences reported.[95]

**Quadrivalent MMRV vaccine**

A single review reported that the proportion of children experiencing at least one adverse event after a second dose was similar between recipients of the MMRV (77.6%) and MMR (78.0%) vaccines, with no vaccine-related serious adverse experiences reported (1 RCT).[95]

#### 5.3.2.2.3 Systemic adverse events (fever and rash)

**Monovalent vaccine**

One review of two-dose monovalent vaccine (Varivax®) noted the most common systemic events reported after a booster dose of varicella vaccine included: upper respiratory infections (44.4%), cough (37.0%), irritability or nervousness (28.6%), disturbed sleep (22.9%) and fatigue (21.7%), while varicella like rashes occurred in 1.0% of all vaccinations (1 RCT).[95] The same review reported that fever (≥38.8C) occurred in 9.4% of all MMR+V recipients and 9.9% of all MMR recipients after a second dose (1 RCT).

**Quadrivalent MMRV vaccine**

A single review reported that in general, systemic adverse events were observed in 37.6 to 66.2% of the study population vaccinated with a second dose of MMRV and 60 to 69.2% of the study population vaccinated with MMR (2 RCTs).[95] However, incidence of fever after the second dose did not differ between groups (3 RCTs, 1 review).[95]

#### 5.3.2.2.4 Febrile seizures

**Quadrivalent MMRV vaccine**

A meta-analysis reported no statistically significant difference in incidence of febrile seizures between MMRV and MMR vaccine recipients, either 0-42 days (pooled RR 0.41 (95% CI: 0.05 to 3.27; 2 RCTs) or 7-10 days after the second dose (pooled RR 0.80 (95% CI: 0.07 to 9.20; 2 RCTs).[112] Similarly, no statistically significant difference in incidence of vaccine-related febrile seizures between MMRV and MMR vaccine recipients was reported, either 0-42 days or 7-10 days after the second dose (pooled RR 0.47 (95% CI: 0.09 to 2.32; 5 RCTs) .[112]

**Quadrivalent MMRV vaccine – co-administration with other vaccines**

A single review reported that no statistically significant difference in incidence of febrile seizures or vaccine-related febrile seizures for the MMRV vaccine when co-administered with other vaccines compared to other vaccines alone (other vaccines not specified) either 0-28/42 days or 7-10 days after vaccination (1 RCT).[112]

#### 5.3.2.3 Two- versus one- dose varicella vaccination

A total of four reviews assessed the safety of two- versus one-dose varicella vaccination,[92, 94, 95, 110] with one review providing a meta-analysis[92] and three reviews providing a narrative synthesis of findings.[94, 95, 110] The monovalent vaccine was assessed in one review[92], the quadrivalent vaccine was assessed in three reviews,[92, 95, 110] and the vaccine type was not clear in one review.[94] One review assessed both monovalent and quadrivalent vaccines.[92] A narrative summary of results by safety outcome measure and vaccine type is provided below.

##### 5.3.2.3.1 Reactions

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

A single systematic review reported that a second dose of varicella vaccine appears to cause fewer reactions than the first (3 studies).[94]

##### 5.3.2.3.2 Local adverse events (pain, redness, swelling)

**Quadrivalent MMRV vaccine**

One review conducted a meta-analysis, reporting the relative risk of pain, redness and swelling for the second dose versus the first dose quadrivalent vaccination.[92] The pooled relative risk for incidence of any pain for the second dose was 0.89 (95% CI: 0.73 to 1.08; 6 self-controlled studies) and Grade 3 pain was 2.05 (95% CI: 0.19 to 22.60; 3 self-controlled studies) up to three days after vaccination.[92] The pooled relative risk for the second dose was 1.00 (95% CI: 0.88 to 1.14; 6 self-controlled studies) for any redness and 4.93 (95% CI: 1.89 to 12.87; 3 self-controlled studies) for Grade 3 redness, up to three days after vaccination.[92] Lastly, the pooled relative risk for incidence of any swelling was 1.34 (95% CI: 1.06 to 1.66; 6 self-controlled studies) and Grade 3 swelling was 1.03 (95% CI: 0.30 to 3.54; 3 self-controlled studies) up to three days after vaccination.[92] A second review also reported that some local symptoms were more frequently reported after the second dose of MMRV (Priorix-Tetra®) compared with the first (interval of four weeks to six months) in most studies (7 RCTs).[110] A third review reported that the overall proportion of subjects with injection-site adverse events was lower (almost half) in subjects who received the second dose of MMRV compared with those who received the first dose (3 RCTs).[95]

#### 5.3.2.3.3 Systemic adverse events (fever and rash)

**Monovalent vaccine**

A single review reported a relative risk for incidence of fever for two- versus one-dose of 0.73 (95% CI: 0.57 to 0.93; 1 self-controlled study) up to 42 days after vaccination.[92]

**Quadrivalent MMRV vaccine**

One review conducted a meta-analysis, reporting the relative risk of fever and rash after the second dose compared with the first dose.[92] For the second dose (comparator first dose), the pooled relative risk for incidence of fever of any intensity was 0.59 (95% CI: 0.54 to 0.64; 5 self-controlled studies) between 0 and 14 days after vaccination and 0.73 (95% CI: 0.69 to 0.71; [sic] 6 self-control studies) between 0 and 42 days after vaccination.[92] For a grade 3 fever or temperature ≥39.5°C, the pooled relative risk for the second dose (versus the first dose) was 0.32 (95% CI: 0.24 to 0.44; 5 self-controlled studies) between 0 and 14 days after vaccination and 0.61 (95% CI: 0.46 to 0.83; 4 self-controlled studies) between 0 and 42 days after vaccination.[92] The pooled relative risk (two- versus one-dose) for incidence of varicella-like rash, 0 to 42 days after vaccination, was 0.32 (95% CI: 0.16 to 0.62; 4 self-controlled studies).[92] An earlier review reported that overall incidence of systemic adverse events was similar among recipients of one- and two-dose MMRV vaccination (3 RCTs).[95]

### 5.3.2.4 Any-dose varicella vaccination

A total of fourteen reviews that assessed the safety of varicella vaccination did not specify the dosing schedule.[91, 94, 95, 106-109, 111, 112, 114-118] Four reviews assessed the monovalent vaccine,[106, 109, 111, 117] seven assessed the quadrivalent vaccine[91, 106, 109, 111, 112, 115, 117] and eight reviews did not specify the vaccine type[94, 95, 106-108, 114, 116, 118] A total of five reviews assessed multiple vaccine types.[91, 106, 109, 111, 117] Two reviews that assessed the quadrivalent vaccine conducted a meta-analysis,[91, 112] while all other reviews provided a narrative synthesis of findings. A narrative summary of results by safety outcome measure and vaccine type is provided below.

#### 5.3.2.4.1 Tolerance (injection site)

**Quadrivalent MMRV vaccine**

A single review noted that the quadrivalent MMRV vaccine is well tolerated when administered either subcutaneously or intramuscularly to children in the second year of life (1 RCT).[106]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

Five-year results from the European Varicella Zoster Virus Identification Programme were noted in one review (2012) and reported that they continue to confirm that Oka/Merck vaccine is generally well tolerated.[106]

#### 5.3.2.4.2 Local adverse events (pain, redness, swelling)

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

A single review noted an increase in local reactions (mild and well tolerated) in vaccine recipients from one RCT, while another smaller trial found no difference, with injection site reactions occurring in 7% to 30% of study participants.[94] A second review noted international experience suggesting that local reactions to the varicella vaccine are possible.[106]

#### 5.3.2.4.3 Systemic adverse events (fever and rash)

**Monovalent vaccine co-administered with another vaccine**

Safety outcomes associated with the administration of the monovalent vaccine with other vaccines were reported in one review.[111] Co-administration of monovalent varicella, MMR and Hib-HepB (Haemophilus Influenzae type b – Hepatitis B) vaccines was compared with separate administration, with co-administration associated with significantly lower incidence of rash (Risk Difference (RD): -5.8%, Relative Risk (RR): 0.6) and less rhinorrhea (RD: -6.1%, RR: 0.7) (1 SR: n=822 children, 1 RCT).[111]

**Monovalent or quadrivalent vaccine (vaccine type unclear)**

One review noted that varicella vaccine recipients showed no increase in rates of fever or varicella-like rash compared with those who received placebo (3 RCTs).[94] A second review reported that the proportion of subjects with systemic adverse events was comparable between MMR+V and MMRV groups compared with MMR groups (5 RCTs).[95] In the same review, the incidence of fever following MMRV or MMR+V vaccination was higher than following MMR vaccination (2 RCTs).[95] Another review conducted at the same time noted international experience suggesting that fever and mild papulovesicular rash are possible adverse effects of the vaccine.[106] In a third review, it was reported that 47.7% of vaccinees (RCT including 507 children vaccinated for varicella) had at least one adverse effect related to the vaccine (most of minor or medium intensity) with fever the most frequent systemic adverse event with a verified relationship with the vaccine.[107] The same review reported results from an observational study covering a 10 year period in the USA. It reported that the most frequent adverse events associated with the vaccine were rash, fever,

injection site reaction and urticaria, with the majority occurring in children aged 12-23 months who had received the vaccine at the same time as other vaccines.[107]

#### 5.3.2.4.4 Seizures and febrile seizures

**Monovalent vaccine**

A single review reported a pooled rate ratio for seizures with the monovalent vaccine co-administered with MMR (versus no vaccination), one to two weeks after vaccination, of 3.13 (95% CI: 2.38 to 4.10, $I^2$ = 0%; n=181,088, 2 self-controlled case series/time person cohort studies; low certainty evidence [GRADE]).[91]

**Quadrivalent MMRV vaccine**

The risk of seizures with the quadrivalent vaccine was reported in five reviews. In the first review, the pooled rate ratio for seizures (versus no vaccination), one to two weeks after vaccination, was reported at 6.08 (95% CI: 4.95 to 7.47, $I^2$=0%; n=180,480, 2 self-controlled case series/time person cohort studies; low certainty evidence [GRADE]).[91] The pooled relative risk for seizures with the quadrivalent MMRV vaccine (versus no vaccination) was reported at 1.50 (95% CI: 1.36 to 1.66, $I^2$=81%; n=2,281,652, 6 cohort studies; low certainty evidence [GRADE]) at 7-10 days after vaccination and 1.53 (95% CI: 1.37 to 1.71, $I^2$=71%; n=1,342,366, 5 cohort studies; low certainty evidence [GRADE]) at 0-42 days after vaccination.[91] A second review demonstrated an approximately 2-fold increase in risk for seizure during 7-10 days (2 cohort studies) and 0-42 days (2 cohort studies) after MMRV vaccination compared with MMR vaccination alone, among children aged 10-24 months.[112] In the same review, similarly an approximately 2-fold increase in risk for febrile seizure 7-10 days (2 cohort studies) and 5-12 days (1 cohort study and 1 matched cohort study) after MMRV vaccination, compared with MMR vaccination, among children aged 10-24 months was demonstrated.[112] However, the review reported no statistically significant difference in risk of seizure between MMRV vaccine recipients and MMR vaccine recipients aged 4 to 6 years, 7-10 days after vaccination (1 cohort study) and 0-42 days after vaccination (1 cohort study).[112] The third review reported insufficient evidence to assess the risk of seizures with the quadrivalent (ProQuad®) vaccine.[109] The fourth review noted international experience suggesting that febrile seizures are possible adverse effects of the quadrivalent MMRV vaccine.[106] A final review, assessing the safety of rubella-containing vaccines, reported a case of a 13 month old girl with high fever one day after MMRV vaccination and seizures six days later.[117]

#### 5.3.2.4.5 Other specific and serious adverse events

**Monovalent vaccine**

A single review conducted for the US Agency for Healthcare Research and Quality (AHRQ), reported increased risk (high strength of evidence [SoE] based on the AHRQ Evidence-based Practice Center grading) of the following adverse events (causal relationship based on mechanistic evidence) associated with monovalent varicella vaccine:

- anaphylaxis
- disseminated Oka VZV without other organ involvement
- vaccine strain viral reactivation without other organ involvement (herpes zoster)
- vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis.[109]

However, estimates of the magnitude of increased risk were not determined.[109] The same review reported insufficient SoE of increased risk of the following adverse events:

- seizures
- acute disseminated encephalomyelitis
- transverse myelitis
- Guillain-Barre syndrome
- small fibre neuropathy
- onset or exacerbation of arthropathy and thrombocytopenia.[109]

**Monovalent vaccine co-administered with another vaccine**

A single review reported no statistically significant difference in adverse events between co-administration and separate administration of the monovalent varicella vaccine and MMR vaccine (3 RCTs).[111]

A review assessing the safety of rubella-containing vaccines reported a case with first episode of temporary sixth nerve palsy after MMR vaccination and a second episode after varicella vaccination.[117] The same review also reported a case of vaccine-induced thrombocytopenic purpura in a 15 month old girl, 12 days after sequential administration of measles, rubella, varicella and mumps vaccination with intervals of four weeks.[117]

### Quadrivalent MMRV vaccine

The review conducted for the AHRQ reported that there was no increased risk (low SoE based on the US AHRQ Evidence-based Practice Center grading) associated with the quadrivalent (ProQuad®) vaccine for acute disseminated encephalomyelitis and death.(109) The same review reported insufficient evidence to assess the risk of the following adverse events with the quadrivalent (ProQuad®) vaccine:

- anaphylaxis or systemic allergic reaction
- ataxia
- febrile seizures
- idiopathic thrombocytopenic purpura
- Kawasaki disease
- meningitis
- seizures and fever.(109)

A second review reported a rate ratio for idiopathic thrombocytopenic purpura was of 2.87 (95% CI: 0.78 to 10.56; 1 self-controlled case series) for the quadrivalent vaccine (versus no vaccination) for children aged nine to 23 months.(91) A review specifically reporting on Kawasaki Disease (KD) cases estimated an incidence rate of one KD case per 11,824 doses of MMRV (1 cohort study), concluding that MMRV was not associated with an increased risk of KD.(115)

### Quadrivalent MMRV vaccine co-administered with another vaccine(s)

A single review compared co-administration of quadrivalent MMRV vaccine and PCV7 (pneumococcal conjugate vaccine seven-valent) vaccine with separate administration and showed significantly less nasopharyngitis (RD: -3.5%, RR: 0.6) and insomnia (RD not reported) after co-administration (n=1027 children, 1 RCT).(111) The same review reported no statistically significant difference in adverse events between co-administration and separate administration for the vaccines detailed in Table 5.3.(111)

### Table 5.3 Vaccines with no statistically significant difference in adverse events between co-administration and separate administration

| Vaccines | Studies | Number of participants |
|---|---|---|
| MMRV + DTaP + Hib-HepB | 1 RCT | n=1,915 children |
| MMRV + DTaP-HepB-IPV/Hib | 2 RCTs | n=1,414 children |
| MMRV or MMR + DTaP-IPV/Hib or DTaP-HepB-IPV/Hib | 1 case-control study | n=590 children |
| MMRV + MenACWY | 1 RCT | n=100 children |
| MMRV + MenC | 1 RCT | n=716 children |

Source: Bauwens J et al. J. Safety of Co-administration versus separate administration of the same vaccines in children: A systematic literature review. Vaccines. 2020;8(1).
**Key:** DTaP: diphtheria, tetanus, and pertussis;
DTaP + Hib-HepB: diphtheria, tetanus, and pertussis + haemophilus influenzae type b conjugate, hepatitis B
DTaP-HepB-IPV/Hib: diphtheria, tetanus, and pertussis, hepatitis B, inactivated poliovirus, haemophilus influenzae type b conjugate
DTaP-IPV/Hib: diphtheria, tetanus, pertussis, inactivated poliovirus, haemophilus influenzae type b conjugate;
MenACWY - quadrivalent meningococcal Group A, C, W-135 and Y conjugate
MenC – meningococcal Group C

A second review noted that co-administration of MMRV with quadrivalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine during the second year of life has shown to be well tolerated, and co-administration of MMRV and Pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) vaccine does not compromise the safety profile of either vaccine (2 RCTs).[106]

#### Monovalent or quadrivalent vaccine (vaccine type unclear)

One of the first systematic reviews conducted (2001) noted that no serious adverse events have been reported in controlled trials, while one post-licensure study found a temporally related serious adverse event rate of 2.9/100,000 doses.[94] In a later review, four serious adverse events were reported after varicella vaccination (one RCT): idiopathic cytopenic thrombus purpura, gastroenteritis, pneumonia and laryngospasm.[107] The study concluded that the vaccine is safe and has a good tolerability profile in children aged 12-15 months.[107] A more recent review (2021) noted few reports and low incidence of serious adverse events associated with the varicella vaccine in RCTs, observational studies and post-marketing surveillance data (moderate certainty evidence [GRADE]).[108]

*Arthritis or arthralgia*

A single review reported on cases of arthritis or arthralgia following varicella vaccination (from 1 cohort study) and concluded that current evidence linking vaccination to incident arthritis or worsening of arthritic conditions is too heterogeneous and incomplete to infer a causal association.[114]

*Herpes zoster*

A number of individual studies, reporting on herpes zoster after varicella vaccination, were included in an early review from 2001.[94] A single RCT reported no cases of

herpes zoster up to nine months after vaccination, one cohort study recorded one mild case in 854 children after vaccination, while seven other cohort studies reported no cases up to 19.5 years after vaccination.(94) The review also reported results from a cohort study where two mild cases were reported in healthy children following vaccination; these data were used to estimate 21 cases/100,000 person-years for Oka/Merck vaccine recipients compared with 77 cases/100,000 person-years for school-aged children following natural chickenpox.(94) The review also included data from the US post-licensure vaccine adverse event reporting system that suggested a rate of 2.6/100,000 vaccine doses distributed, while a population based study found a rate of 42/100,000 in unvaccinated children (20/100,000 population in children less than five years old).(94)

*Stevens Johnson Syndrome (SJS)*

A single review assessing SJS in vaccinated individuals reported a case in a 27 month old baby (not reported whether the infant was immunocompetent or not) following the administration of varicella vaccine (1 study and case review).(116) However, the review concluded that a causal link between vaccination and SJS cannot be established by this study.(116)

*Varicella reactivation meningitis*

A recent (2021) review reported nine cases (eight had one dose and one had two doses) of varicella reactivation meningitis post varicella vaccination with a mean interval of 5.6 years (standard deviation 2.9 years) since vaccination; all nine cases reported full recovery without neurological sequelae.(118)

*Varicella transmission from vaccinated individuals*

A 2001 review reported that no clinical trials have shown transmission of vaccine related VZV between immunocompetent individuals while case reports of transmission from children with varicella-like rash after vaccination have been reported rarely.(94)

*Death*

Of the two reviews (published in the same year) that reported on deaths, but were not clear on vaccine type, the first review noted that there do not appear to be any reported deaths due to the varicella vaccine.(106) The second review noted that although some deaths have been reported after vaccination in a 10 year (1995 to 2005) observational study in the USA, a consistent association has not been proven.(107)

### 5.3.3 Quality Appraisal

The majority of reviews had multiple methodological flaws with one review deemed 'high' quality,[91] two reviews deemed 'low' quality[109, 116] and 14 reviews deemed 'critically low' quality.[92, 94, 95, 106-108, 110-115, 117, 118] None of the 'critically low' quality reviews included a protocol or explicit statement that the review methods were established prior to the conduct of the review. The search strategies were not considered comprehensive in 15 reviews, lacking searches of reference lists and grey literature, not providing justification for foreign language exclusions, not providing clear dates for searches or not publishing within two years of the search end date.[92, 94, 95, 106-111, 113-118] A list of excluded studies and reasons for exclusions were provided for three reviews only.[91, 95, 109] Included studies were fully described in adequate detail in four reviews only.[91, 95, 112, 114] A total of nine reviews either did not conduct a risk of bias assessment of individual studies included in the review or where it was indicated that it was conducted, the tool used was not clear and results were not provided.[95, 106-108, 111, 113-115, 118] The full set of results for the quality appraisal are provided in the supplementary file (Appendix A5.3).

### 5.3.4 Overlap within included reviews

Overlap calculations were calculated based on 16 reviews, as primary publications were not identifiable in one review.[92] Although RCTs were not identifiable in another review, the review was included in overlap calculations as other primary studies/reviews were identifiable.[112] A total of 119 primary publications were identified in 16 reviews, with 96 index publications (primary publications that are counted on their first occurrence only).[89] The total of 96 index publications included 34 RCTs and 62 other primary studies/reviews. Nine RCTs were included in more than one review, and 11 other primary studies/reviews were included in more than one review. The overall corrected covered area was calculated at 1.6, indicating slight overlap.[89]

## 5.4 Discussion

Overall, 17 systematic reviews that assessed the safety of varicella vaccination were included in this overview of reviews. While the majority of reviews contained methodological flaws and only one review was deemed 'high' quality,[91] it is noted that that there is substantial evidence underpinning the safety of varicella vaccination, comprising 34 RCTs and 62 other primary studies/reviews.

### 5.4.1 Local adverse events (pain, redness and swelling) and tolerability

Evidence for the monovalent vaccine was limited to reports of higher incidence of local adverse events with one-dose monovalent administered with MMR, compared

to MMR only.[95] However this was not the case with the quadrivalent vaccine, with no significant differences in incidences of pain, redness, swelling between MMRV and MMR groups.[95, 110] While no data were reported with regard to two-dose monovalent specifically, the quadrivalent vaccine was reported to be well tolerated as part of a two-dose regime.[106, 110]

Directly comparing one- and two-dose, an early review, likely to be reporting the monovalent vaccine given the timing of the review, (although the vaccine type was not reported) noted that a second dose of varicella vaccine appears to cause fewer reactions than the first.[94] For the quadrivalent vaccine, the evidence was mixed with some reviews reporting higher relative risk (for two- versus one-dose) and higher frequency for some local symptoms,[92, 110] and another reporting that the overall proportion of subjects with injection-site adverse events was lower (almost half) in subjects who received the second dose of MMRV compared with those who received the first dose.[95]

Overall, the evidence suggests that some local reactions (typically mild) are possible after one- and two-dose monovalent and quadrivalent vaccination, but at levels that would be considered acceptable for a vaccination/immunisation programme.

### 5.4.2 Systemic adverse events (fever and rash)

While fever and rash may occur more frequently in one-dose MMR+V recipients than MMR recipients,[95] statistically significantly higher incidences of fever and rash (pooled RRs ranged from 1.19 to 1.60) were reported for one-dose MMRV recipients compared with MMR recipients, up to 43 days after vaccination.[110] However, with two-dose vaccination, observed systemic adverse events were lower in MMRV groups than MMR groups in general, but incidence of fever did not differ.[95] Similar incidence of systemic adverse events were reported in one- and two-dose MMRV recipients.[95]

Directly comparing first and second dose (self-controlled studies), a lower relative risk for incidence of fever (0.73) was reported with the second dose monovalent vaccine and [92] a lower relative risk for both fever (0.73) and varicella-like rash (0.61) was reported with the second dose quadrivalent vaccine.

While the evidence suggests that the rates of systemic adverse events overall are generally comparable between varicella vaccinated groups and MMR vaccinated groups or placebo groups, rates of fever in particular may be higher in MMR+V groups and MMRV groups compared to MMR groups.[94, 95] Additionally, the relative risk for systemic adverse events may be lower after the second dose (both monovalent and quadrivalent) compared with the first dose.[92]

### 5.4.3 Seizures and febrile seizures

No data on seizures were reported for either one- or two-dose monovalent vaccination, while a single review, that didn't specify the dosage, reported a risk ratio of 3.13 for seizures with the monovalent vaccine administered with MMR, compared with no vaccination (low certainty evidence).[91] RCT data for both one- and two-dose quadrivalent MMRV suggests that the risk of febrile seizures and vaccine-related febrile seizures is not statistically significantly different between MMRV recipients and MMR recipients.[112] However, in two further reviews where the dosage was not specified,[91, 112] the observational evidence suggests a greater risk of seizure/febrile seizures after MMRV vaccination compared with MMR vaccination alone, from five days up to approximately 42 days after vaccination in one review.[91] The evidence was deemed 'low certainty' in one of these reviews.[91] While it was also reported that there was insufficient evidence to assess the risk of seizures with the quadrivalent (ProQuad®) vaccine,[109] overall the evidence suggests that febrile seizures are possible adverse effects of the quadrivalent MMRV vaccine.

### 5.4.4 Other adverse events

An association was reported in one review (causal relationship based on mechanistic evidence; high strength of evidence) between the monovalent vaccine and anaphylaxis, disseminated Oka VZV without other organ involvement, vaccine strain viral reactivation without other organ involvement (herpes zoster), vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis, although the magnitude of increased risk has not been estimated.[109] On the risk of herpes zoster, the evidence was mixed with one review reporting low case numbers (vaccine type not specified)[94] and another review reporting that at an individual study level, most studies suggest that the risk of herpes zoster following a single dose quadrivalent varicella vaccination is lower than the risk following wild-type varicella infection.[106]

Evidence on the risk of idiopathic thrombocytopenic purpura with the quadrivalent vaccine was mixed, with one review reporting insufficient evidence to assess the risk[109] and another reporting a rate ratio of 2.87 for the quadrivalent vaccine (versus no vaccination) for children aged nine to 23 months.[91] No association between the vaccine and death were reported.

### 5.4.5 Co-administration of the varicella vaccine with other vaccines

A number of reviews reported limited data on co-administration of varicella vaccines with other vaccines versus separate administration.[106, 111, 112, 117] Co-administration was not associated with an increased risk of any adverse event and the evidence suggests it does not compromise the safety profiles of the vaccines. Lower relative

risks of some adverse events were reported with co-administration. These included significantly less rash and rhinorrhea for co-administration of the monovalent varicella (dosage not reported), MMR and Hib-HepB vaccines and significantly less nasopharyngitis and insomnia for co-administration of the quadrivalent MMRV vaccine and PCV7.[111]

### 5.4.6 Case reports

A number of reviews provided cases reports of specific rare, serious adverse events following varicella vaccination. These adverse events included arthritis/arthralgia,[114] Kawasaki Disease,[115] Stevens Johnson Syndrome,[116, 118] and varicella reactivation meningitis,[102] with no association with varicella vaccine (monovalent or quadrivalent) reported.

### 5.4.7 Strengths and Limitations

The main strength of this overview of reviews is that it provides a comprehensive synthesis of the published and unpublished evidence on the safety of varicella vaccination since the development of the varicella vaccine in the 1970s. The overview captures changes in vaccine development and varying programmes of administration, including differing dosing schedules, over time. The overview search involved a comprehensive electronic database and grey search and was conducted without date and language restriction to ensure that all possible relevant reviews were identified. The evidence from the included reviews originates from many regions and countries across the globe, ensuring that the results are broadly generalisable.

However, there are a number of important limitations. Firstly, although 17 systematic reviews were included in this overview of safety, overall, the quality of reviews was largely deemed ‘critically low’. With the exception of one review, all reviews had methodological flaws which lowers the certainty of the evidence. It should be noted however, that although the quality of reviews was largely ‘critically low’, the quality of the underpinning primary studies, including 34 RCTs, could not be ascertained as risk of bias assessments were not conducted for many reviews. Additionally, the source of evidence in half of the systematic reviews was solely observational, raising potential issues with bias and confounding. Lastly, with regard to serious adverse events specifically, it should be noted that RCTs are generally underpowered to detect differences in these rates between groups, while observational studies are often not suitable for determining a difference between groups.

There were also a number of issues that hampered the comparison between reviews and the synthesis across reviews. For both types of reviews, that is those that

included a meta-analysis and those that included a narrative summary of findings only, the reporting of some of the systematic reviews lacked critical detail. This included lack of detail on vaccine type administered, dosing-schedule, and follow-up period after vaccination. There was also limited evidence on co-administration of the varicella vaccine with other vaccines. In some instances there was a lack of clarity in terms of the severity of the adverse reaction to the vaccine; for example, where a six-fold difference in reported incidence rates of fever between trials, related most likely to some reviews reporting any fever and others reporting fever >39°C. From a policy perspective, the lack of detailed reporting and evidence gaps impact on the ability to fully inform policy decisions where the introduction of universal varicella vaccination is being considered or where existing universal varicella vaccination programmes are under review.

### 5.4.8 Conclusion

The aim of this overview of reviews was to establish the clinical safety of potential varicella vaccination strategies by synthesising the evidence available from relevant systematic reviews that have been published to date. While the analysis by vaccine type and dosing strategy was restricted due to lack of detail in reporting of the systematic reviews, overall, there was clear and consistent evidence from a substantial evidence base, comprising 34 RCTs and 62 other primary studies/reviews, that that both monovalent and quadrivalent varicella vaccination are safe. The evidence suggests that mild local and systemic reactions, such as fever and rash, are relatively common, and while febrile seizures are possible adverse effects of both the monovalent and quadrivalent MMRV vaccine, serious adverse events are rare. The limited evidence on the co-administration of the varicella vaccine with other vaccines suggests that co-administration does not compromise the safety of the vaccines. The potential harms associated with varicella vaccination must be considered in light of the clinical benefits associated with reduced rates of varicella zoster virus infection and incidence of varicella disease.

# 6 Review of methodology for economic modelling studies of childhood varicella vaccination

## Key points

- The most recent systematic review of economic modelling studies of routine varicella vaccination (VV) in high income countries was published in 2015. To establish and assess the most up to date international evidence on the approaches taken to the economic modelling of universal childhood varicella vaccination, a rapid review of studies published since 2015 was undertaken.
- Nine additional studies were identified in the rapid review, eight of which were conducted for European countries. Five studies were funded by industry, two by government agencies, one by a research body, and one declared no funding.
- Eight studies employed dynamic transmission modelling, using a series of ordinary differential equations, to estimate the impact of VV on varicella zoster virus transmission, while one used a dynamic Markov model. This compared with the use of dynamic transmission modelling in 13 of 23 studies in the 2015 systematic review.
- Seven studies took account of the exogenous boosting theory and modelled the impact of VV on incidence of herpes zoster (shingles). Most studies included in the earlier systematic review were reported to have ignored the relationship between varicella and herpes zoster.
- Similar to the earlier review, the analysis was conducted from both the healthcare payer and societal perspectives in the majority of studies (n=7), with the tax payer and societal perspectives adopted in one study each.
- While overall the appraisal did not raise major concerns with the quality of included studies, there were some concerns with regard to structural assumptions, 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 when developing economic models of routine VV, all of which will be considered in the development of a de novo economic model of VV for Ireland.

## 6.1 Introduction

This chapter reviews the published international evidence on economic evaluations of childhood varicella vaccination to inform the economic modelling and assessment of cost effectiveness in Ireland. The review specifically examines the approaches taken to modelling the expected costs and benefits of universal childhood varicella vaccination.

## 6.2 Background

A total of 13 different considerations have been identified for modelling and health economic evaluation of vaccination programmes specifically; these include

- model selection
- time horizon of models
- natural disease history
- measures of vaccine-induced protection
- duration of vaccine-induced protection
- indirect effects apart from herd protection
- target population
- model calibration and validation
- handling uncertainty
- discounting
- health-related quality of life
- cost components
- perspective adopted.[119]

A scoping exercise was undertaken to identify published systematic reviews of economic evaluations of universal childhood varicella vaccination that provide detail on the economic models employed and the model input parameters. A total of five systematic reviews were identified,[120-124] with heterogeneity observed in a number of aspects of the economic evaluations, including the perspective adopted, type of model, modelling of waning immunity, assessment of indirect costs, modelling the effect of varicella vaccination on herpes zoster, and estimation of the efficacy parameters.[121, 123, 124]

The most recent systematic review, published in 2015 and comprising a search of the PubMed database up until October 2013, assessed the cost effectiveness of routine varicella and herpes zoster vaccination in high-income countries estimated by

modelling studies.[123] 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. The review included 23 studies that evaluated the cost effectiveness of varicella vaccination and provided relevant data on the type of model employed, model input parameters, vaccination strategy, vaccine characteristics and economic results. However, given the timing of the review, most of the studies considered a one-dose vaccination schedule only. Additionally, data that would be relevant when modelling the costs and benefits of varicella vaccination, but were not reported in the review, include indirect costs (type of cost and method of measurement and valuation) where a societal perspective was adopted, and utility values (relevant effect and data source) where a cost-utility analysis was conducted.

In order to establish the most up to date evidence of the models employed and parameters used for the economic evaluation of childhood varicella vaccination, a rapid review was conducted. The rapid review sought to identify economic evaluations of childhood varicella vaccination that have been published in the nine year period from 2013 (to cover the last search date for the most recent systematic review) to June 2022. 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 childhood varicella vaccination.

## 6.3 Rapid review methods

### 6.3.1 Research question

*Research question:* What approaches have been used to model the expected costs and benefits of childhood varicella vaccination?

The following Population, Interest, Context (PICo) framework was developed to address the above research question (Table 6.1).

### 6.3.2 Eligibility criteria

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

### Table 6.1 PICo for rapid review of methodology for economic modelling studies of childhood varicella vaccination

| | |
|---|---|
| **Population** | Immunocompetent children aged 9 months to 6 years receiving varicella vaccination |
| **Interest** | Approaches to modelling the expected costs and benefits of universal varicella vaccination, including, but not limited to:<br>▪ Model structure<br>o Type of model<br>o Perspective adopted<br>o Time horizon<br>o Age at vaccination<br>o Dosing schedule<br>o Vaccine type<br>o Comparator<br>o Waning immunity<br>▪ Model input parameters<br>o Vaccine efficacy or effectiveness<br>o Vaccination coverage<br>o Direct and indirect costs<br>o Direct and indirect effects<br>o Utility values for cost-utility analysis<br>▪ Model outputs<br>o Economic results that include a ratio of (incremental) costs to (incremental) benefits. |
| **Context** | Universal childhood varicella vaccination programmes in high income countries‡ |

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

## 6.3.3 Search strategy

A comprehensive electronic search was conducted in Medline (EBSCO) and Embase (Ovid) from 2013 to 28 June 2022, along with a forward citation search of the most recent systematic review.[123] The database search strings, developed in consultation with an information specialist, dates of searches and search results are provided in Appendix A6.1 and are publicly available on Zenodo via this link.

## 6.3.4 Study selection, data extraction and management

Results were exported to Covidence software[86] 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 6.1 and section 6.2.2. 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.

### 6.3.5 Data extraction and quality appraisal

Table 6.2 details the data that were extracted for each included study. In line with the systematic review that has been updated, critical appraisal of all included studies was undertaken using the framework for quality assessment of decision-analytic models proposed by Philips et al.[125] The framework assesses the quality of models under three key themes; *Structure, Data and Consistency*.

**Table 6.2 Data extracted from each included study**

| | |
|---|---|
| **General study characteristics** | ▪ author name<br>▪ year of publication<br>▪ country<br>▪ type of economic evaluation<br>▪ population<br>▪ funding source |
| **Model characteristics** | ▪ model type<br>▪ perspective<br>▪ time horizon<br>▪ comparator<br>▪ discount rates for costs and outcomes |
| **Intervention and vaccination strategy** | ▪ vaccine type (monovalent or quadrivalent measles mumps rubella varicella [MMRV])<br>▪ age at vaccination<br>▪ dosing schedule<br>▪ coverage rate |
| **Vaccine characteristics** | ▪ efficacy or effectiveness<br>▪ waning of immunity |
| **Direct costs**<br>**Indirect costs** | ▪ type of costs included<br>▪ methods of measurement and valuation |
| **Direct effects including long-term effects (e.g. herpes zoster)**<br>**Indirect effects (e.g., herd immunity and impact on incidence of herpes zoster in others)** | ▪ type of effects included<br>▪ methods of measurement and valuation |
| **Economic results** | ▪ type of summary ratio<br>▪ overall health care perspective result<br>▪ overall societal perspective result<br>▪ authors' conclusions |

### 6.3.6 Data synthesis

Summary characteristics of included studies and the vaccination strategies and vaccine characteristics 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 and this 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.[84]

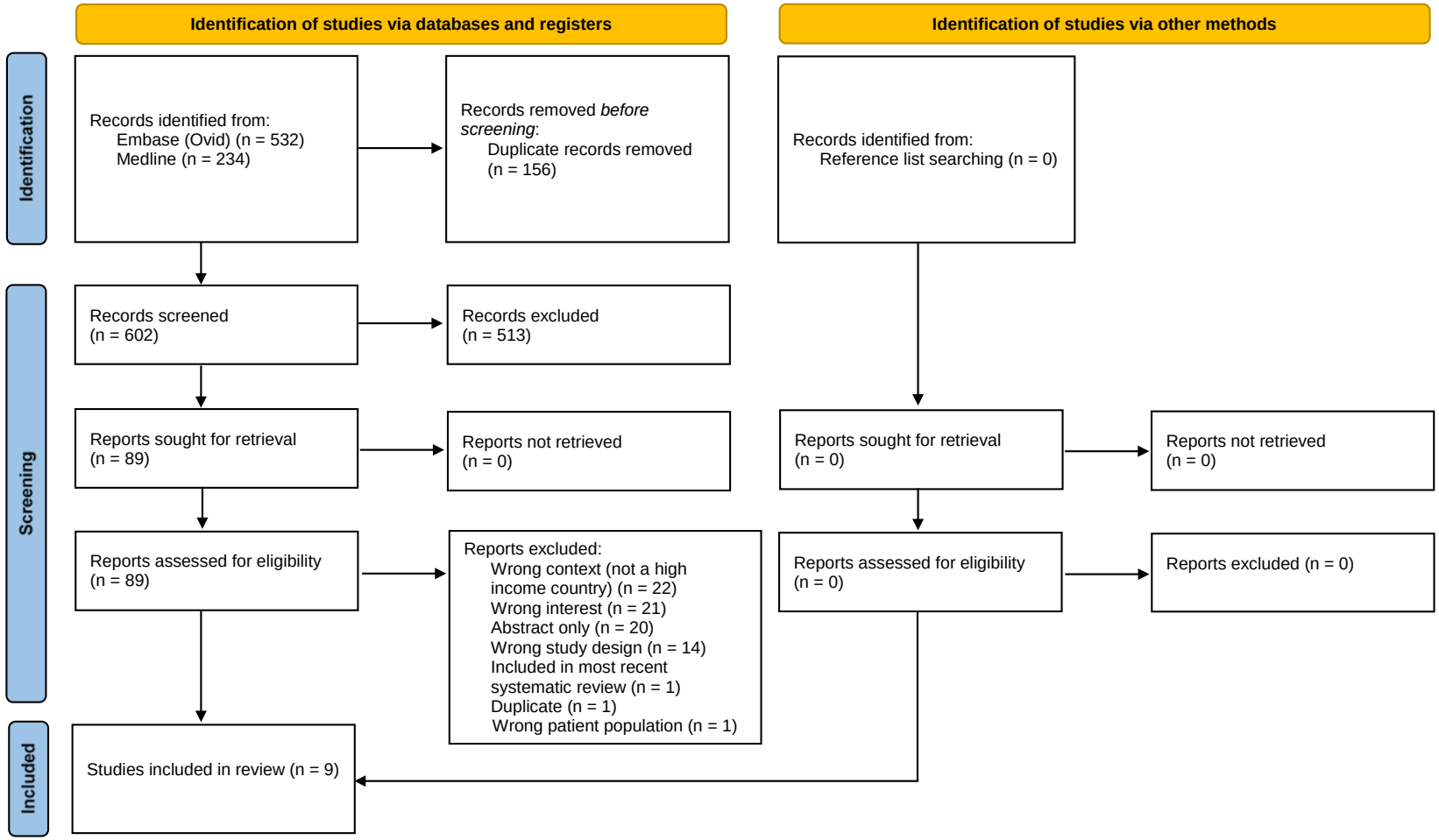
## 6.4 Results

Following the removal of duplicates, the database searches identified a total of 602 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 89 articles remained for full text review. Following full text review and subsequent exclusion, nine studies remained for inclusion in this rapid review (Figure 1). Full data extraction tables for included studies are provided in Appendix A6.2.

### 6.4.1 Characteristics of included studies

A total of nine model-based studies, mostly performed for European countries, were identified that met the inclusion criteria for this rapid review. A single study was conducted for each of Canada (Alberta),[126] France,[127] the Netherlands,[128] Norway,[129] Sweden,[130] Switzerland,[131] and the UK,[132] with two studies conducted for Italy.[133, 134] An overview of general study characteristics and information on the modelling framework for included studies is provided in Table 6.3. All studies conducted a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA), including one that conducted both a CUA and a cost-benefit analysis (CBA).[132] Five of the nine studies (UK, one for Italy, France, Norway and Switzerland) were industry funded,[127, 129, 131-133] two were funded by government agencies (Alberta, Canada and the Netherlands),[126, 128] one was funded by a research body (Italy),[134] and one declared no funding, but author affiliations included a public health agency and academia (Sweden).[130]

## Figure 6.1 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/

## Table 6.3 General study characteristics of included studies

| Study | Year | Country | Model type | Impact of varicella vaccination on herpes zoster incidence (exogenous boosting) | Time horizon (base case) | Type of economic evaluation | Perspective | Discount rate (costs/health effects) | Funding source |
|---|---|---|---|---|---|---|---|---|---|
| Akpo et al.[132] | 2020 | UK | Dynamic transmission | Yes | 20yrs, 40yrs, 100yrs | CBA; CUA | Health care payer; societal | 3.5%/3.5% | Industry |
| Azzari et al.[133] | 2020 | Italy | Age-structured deterministic dynamic transmission | No | 50yrs | CEA | Health care payer; societal | 3%/3% | Industry |
| Heininger et al.[131] | 2021 | Switzerland | Age-structured deterministic dynamic transmission | No | 50yrs | CUA | Health care payer; societal | 3%/3% | Industry |
| Littlewood et al.[127] | 2015 | France | Age-structured dynamic transmission | Yes | 80yrs | CEA | Health care payer; societal | 4%/4% until 30yrs after vaccination; 2%/2% from 30yrs after vaccination | Industry |
| Melegaro et al.[134] | 2018 | Italy | Stochastic individual-based | Yes (both temporary complete immunity and progressive partial immunity) | 25yrs, 50yrs, 85yrs | CUA | Taxpayer | 3%/3% | Research body |
| Pawaskar et al.[129] | 2021 | Norway | Age-structured deterministic dynamic transmission | Yes (assumed temporary full immunity) | 50yrs | CUA | Health care payer; societal | 3%/3% | Industry |
| Rafferty et al.[126] | 2021 | Alberta, Canada | Agent based | Yes | 75yrs | CUA | Health care payer; societal | 1.5%/1.5% | Government |
| van Lier et al.[128] | 2015 | the Netherlands | Age-structured dynamic transmission | Yes | up to 180yrs | CEA | Societal | 4%/1.5% | Government |
| Wolff et al.[130] | 2021 | Sweden | Age-structured dynamic markov | Yes (assumed comparable to live herpes zoster vaccination of limited duration) | 85yrs | CUA | Health care payer; societal | 3%/3% | Independent |

Key: CBA - cost-benefit analysis: CEA - cost-effectiveness analysis; CUA - cost-utility analysis;

### 6.4.2 Model characteristics of included studies

*Model*

Six studies employed a dynamic transmission model to model the impact of varicella vaccination.[127-129, 131-133] The remaining three studies employed an agent-based model,[126] an individual-based model,[134] and a dynamic Markov model.[130] Details of model calibration (and validation in some cases) were described in six of the nine studies.[126, 127, 131-134] Data on social contact patterns for seven studies[126-128, 130-132, 134] were sourced or derived from, or validated using data from the POLYMOD (Improving Public Health Policy in Europe through Modelling and Economic Evaluation of Interventions for the Control of Infectious Diseases) study.[135] Social contact patterns were derived assuming proportionate mixing (i.e., mixing between age groups is proportional to their activity level) in a further study (no further detail provided),[133] and no detail on social contact patterns was reported in another study.[129]

*Time horizon*

All studies adopted a time horizon of at least 50 years[129, 131, 133] and up to 85 years,[129] or included a short- (20 to 25 years), medium- (40 to 50 years) and long-term (85 to 100 years) horizon for the base case analysis.[132, 134]

*Perspective*

A total of seven studies conducted the analysis from both the payer and societal perspectives,[126, 127, 129-133] while one conducted the analysis from the societal perspective only[128] and one adopted the perspective of the tax-payer.[134]

*Discount rates*

Discount rates were applied in accordance with national guidelines in all nine studies. The same rates were applied for both costs and outcomes in seven studies,[126, 129-134] ranging from 1.5% for Alberta, Canada[126] to 3.5% for the UK.[132] In the study conducted for the Netherlands, differential discounting was applied with a discount rate of 4% for costs and a rate of 1.5% for health effects.[128] In the study conducted for France, a discount rate of 4% was applied up until 30 years after vaccination and 2% from 30 years after vaccination.[127]

### 6.4.3 Intervention and vaccination strategies

Table 6.4 provides a summary of the varicella vaccination strategies and vaccine characteristics considered in the models. All nine studies assessed a two-dose strategy with varying use of the monovalent and quadrivalent vaccines as follows:

- one study assessed the monovalent vaccine for both doses[128]
- one study assessed the quadrivalent vaccine for both doses[127]
- in three studies the vaccine type varied between the first and second dose[129, 131, 132]
- one study assessed two strategies; the quadrivalent vaccine for both doses and the monovalent vaccine for the first dose with the quadrivalent vaccine for the second dose[133]
- the type of vaccine was not reported in three studies.[126, 130, 134]

Five of the nine studies assessed a strategy with a fixed age at vaccination,[127, 128, 130, 133, 134] while four studies assessed strategies with varying ages at vaccination.[126, 129, 131, 132] Three of these four studies specifically assessed both short- and long-dose intervals[126, 129, 131] and one study assessed a one month difference in the timing of the first dose (related to the administration of either the monovalent or quadrivalent vaccine).[132]

Age at first dose ranged from nine months[131] to 15 months,[128, 129, 133, 134] while age at second dose ranged from 12 months[131] to 11 years.[129] Of the five studies that assessed a strategy with a fixed age at vaccination, two assessed a short-dose interval of six months (France and Sweden) [127, 130] and three assessed a long-dose interval of at least three years (Italy [n=2] and the Netherlands).[128, 134] Of the four studies that assessed strategies with varying ages at vaccination, one study assessed multiple intervals ranging from three months to 15 months (Switzerland),[131] one study varied the first dose by one month maintaining a long dose interval of approximately two and half years for both strategies (UK),[132] and two studies assessed both short- (up to six months) and long-dose intervals (up to 10 years approximately) (Norway and Alberta, Canada).[126, 129]

In general, coverage rates modelled ranged from 80% to 95%. A single coverage rate was used for both doses in four studies, ranging from 80% (Italy)[134] to 95% (Norway, the Netherlands and Sweden).[128-130] In reviews where coverage rates differed by dose, rates of 95% and 90% (Switzerland) and 90% and 80% (France) were used for first and second dose, respectively. A further two reviews used different coverage rates depending on vaccine type. For the UK model, coverage rates of 87% and 95% were used for first dose monovalent and quadrivalent vaccine, respectively, while a rate of 87% was used for the second dose

(quadrivalent only).[132] For the second Italian model, coverage rates of 81% and 85% were used for first dose monovalent and quadrivalent vaccine, respectively, while a rate of 83% was used for the second dose (quadrivalent only).[133] In the final review, where an agent-based model was used, agents were designated as vaccine 'rejectors', 'hesitants' or 'acceptors'. Coverage rates varied by designation and dose, ranging from 3% for 'rejectors' to 97% for 'acceptors' for the first dose and 33% for 'rejectors' to 98% for 'acceptors' for the second dose (conditional on receipt of the first dose).[126]

### 6.4.4 Vaccine characteristics

The use of efficacy/effectiveness data and the rates applied varied considerably between studies. Efficacy data were used in five studies,[127, 129, 132-134] effectiveness data were used in three studies,[126, 128, 130] although one study did not report the rates applied,[126] and one study did not report the type of data used or rates applied.[131] In three of the five studies that used efficacy data, different rates were used for both one dose and two doses of two different manufacturer's vaccines.[129, 132, 133] For vaccines manufactured by GSK, efficacy rates used for one dose varied from 61.7% to 67.3% and efficacy rates used for two doses varied from 94.6% to 95.4%. For vaccines manufactured by MSD, efficacy rates used for one dose varied from 78% to 100% and efficacy rates used for two doses varied from 97% to 100%. A further study used an efficacy rate of 80% for one dose and 96% for two doses,[134] while the fifth study reported a single efficacy rate of 95% for two doses.[127] For the two studies that reported using effectiveness data and supplied the rates used, rates of 81% and 92%[130] and 90% and 95%[128] were used for one dose and two doses, respectively.

Waning of immunity was considered and waning rates were provided in five studies.[127, 129, 130, 132, 133] Waning rates for both one and two doses were provided in all five reviews and varied from 2% to 5.88% per annum for one dose and from 1.3% to no waning for two doses. A single review reported separate waning rates for GSK and MSD vaccines.[133] Waning of immunity was not considered in one study [128] and was not reported in three further studies.[126, 131, 134]

## Table 6.4 Vaccination strategies and vaccine characteristics considered in the models evaluating routine varicella vaccination

| Study | Year | Dosing schedule | Vaccine type | Age at vaccination | Vaccine efficacy/ effectiveness | Waning rate (per year) | Vaccination coverage |
|---|---|---|---|---|---|---|---|
| Akpo et al.[132] | 2020 | 2-dose | 1st dose mono/quad,<br>2nd dose quad | 1st dose at 13mths (mono), 2nd dose at 3yrs 4mths (quad);<br>1st dose at 12mths (quad), 2nd dose at 3yrs 4mths (quad) | Efficacy GSK:<br>1-dose 67.2%, 2-dose 95.4%<br>Efficacy MSD:<br>1-dose 78%, 2-dose 98.3% | 1st dose 0.03,<br>2nd dose none | 1st dose 87%,<br>2nd dose 87% (mono + quad);<br>1st dose 95%,<br>2nd dose 87% (quad + quad) |
| Azzari et al.[133] | 2020 | 2-dose | 1st dose quad,<br>2nd dose quad;<br>1st dose mono,<br>2nd dose quad | 1st dose at 13-15mths (mono/quad),<br>2nd dose at 5-6yrs (quad) | Efficacy GSK:<br>1-dose 65.4%, 2-dose 94.9%<br>Efficacy MSD:<br>1-dose 100%, 2-dose 100% | MSD:<br>1st dose 0.04,<br>2nd dose 0.013<br>GSK:<br>1st dose 0.0588,<br>2nd dose none | 1st dose mono 81%,<br>1st dose quad 85%,<br>2nd dose quad 83% |
| Heininger et al.[131] | 2021 | 2-dose | 1st dose quad,<br>2nd dose mono/quad | 1st dose at 9mths (quad),<br>2nd dose at 12mths (quad);<br>1st dose at 12mths (quad),<br>2nd dose at 19mths (quad);<br>1st dose at 9mths (quad),<br>2nd dose at 24mths (mono); | NR | NR | 1st dose 95%,<br>2nd dose 90% |
| Littlewood et al.[127] | 2015 | 2-dose | 1st dose quad,<br>2nd dose quad | 1st dose at 12mths;<br>2nd dose at 18mths | Efficacy:<br>2-dose 95% | 1st dose 0.0588,<br>2nd dose none | 1st dose 90%,<br>2nd dose 80% |
| Melegaro et al.[134] | 2018 | 2-dose | NR | 1st dose at 15mths;<br>2nd dose at 5-6yrs | Efficacy:<br>1-dose 80%, 2-dose 96% | NR | 80% |
| Pawaskar et al.[129] | 2021 | 2-dose | 1st dose mono,<br>2nd dose mono/quad | 1st dose at 15mths;<br>2nd dose at 18mths/7yrs/11yrs | Efficacy GSK:<br>1-dose 61.7%, 2-dose 94.6%<br>Efficacy MSD:<br>1-dose: 90.3%, 2-dose 97% | 1st dose 0.04,<br>2nd dose 0.013 | 95 to 97%<br>(base case value not clear) |
| Rafferty et al.[126] | 2021 | 2-dose | NR | 1st dose at 12mths;<br>2nd dose at 18mths/4-6yrs | Real world effectiveness<br>(data NR) | NR | 1st dose: Rejectors (3%), Hesitants (75%), Acceptors (97%);<br>2nd dose: Rejectors (33%), Hesitants (82%), Acceptors (98%) |
| van Lier et al.[128] | 2015 | 2-dose | 1st dose mono,<br>2nd dose mono | 1st dose at 15mths;<br>2nd dose at 4yrs | Effectiveness:<br>1-dose 90%, 2-dose 95% | Not considered | 95% |
| Wolff et al.[130] | 2021 | 2-dose | NR | 1st dose at 12mths;<br>2nd dose at 18mths | Effectiveness:<br>1-dose 81%, 2-dose 92% | 1st dose 0.02,<br>2nd dose none | 95% |

Key: NR – not reported

### 6.4.5 Costs (direct and indirect)

*Direct costs*

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

- GP visits for varicella and herpes zoster (herpes zoster) (wildtype and breakthrough)
- outpatient visits for varicella and herpes zoster (wildtype and breakthrough)
- hospitalisation for varicella and herpes zoster (wildtype and breakthrough) including hospitalisation for stroke as a result of herpes zoster
- prescription and over-the-counter drugs for outpatients and inpatients (varicella and herpes zoster [with and without post herpetic neuralgia (PHN)])
- diagnostic tests for outpatients and inpatients
- personal costs, e.g., travel and gifts
- vaccination costs
    - vaccine
    - vaccine introduction cost (e.g., campaign, new leaflets)
    - vaccine co-ordination cost (e.g., variable personnel costs, materials, printing)
    - administering the vaccine
    - extra time required to administer the monovalent vaccine
    - delivery and cold-chain of the monovalent vaccine
    - GP visits related to vaccine adverse events (excluding febrile seizures)
    - emergency room visits related to vaccine adverse events (febrile seizures).

*Indirect costs*

Indirect costs included in the economic modelling mainly included the following:

- productivity losses for those with varicella and or herpes zoster (wildtype and breakthrough) and for caregivers of those with the disease.
- additional cost of alternative childcare arrangements.

Data required to measure and value costs (both direct and indirect), where reported, are included in the data extraction tables.

### 6.4.6 Effects (direct and indirect)

*Direct effects*

Across all studies, the direct effects of vaccination included in the economic modelling generally incorporated some or all of the following, with varicella and herpes zoster stratified in some studies by wildtype or breakthrough disease and by age:

- incidence of varicella
- incidence of herpes zoster with and without PHN
- outpatient cases of varicella and herpes zoster
- hospitalised cases of varicella and herpes zoster
- incidence of complications for hospitalised cases of varicella
- deaths associated with varicella and herpes zoster
- vaccine-induced VZV reactivation (one study only).[128]

Data required to measure and value direct effects where reported, are included in the data extraction tables in Appendix 2.

*Indirect effects*

Seven of nine studies included and modelled the impact of varicella vaccination on incidence of herpes zoster associated with exogenous boosting.[126-130, 132, 134] The theory of exogenous boosting posits that sub-clinical reactivation of the VZV, due to exposure to infectious individuals with varicella, provides a boost to immunity helping to prevent reactivation of the latent virus and the development of herpes zoster.[136] Assumptions with regard to the impact of varicella vaccination on incidence of herpes zoster (due to exogenous boosting) varied. In the three studies that provided data on the assumed duration of boosting, the duration varied considerably and included two years in the UK study,[132] five years (based on empirical data) in the Canadian study,[126] and 80 years in the study conducted for Norway.[129] The review for Sweden noted that the impact of exogenous boosting was assumed to be comparable to live herpes zoster vaccination with a limited duration of immunity and was modelled as a form of complete immunity to herpes zoster that wanes with time.[130] Other assumptions around exogenous boosting that were clearly specified in the studies included the following:

- the study for France assumed partial age-specific boosting with the probability of being boosted equal to the estimated age-specific efficacy of the herpes zoster vaccine[127]

- two scenarios were assessed in one of the studies for Italy; temporary complete immunity, where each boosting event provides partial complete immunity to herpes zoster and progressive partial immunity, where each boosting event progressively reduces the risk of VZV reactivation. The rate of VZV reactivation decreases with the number of re-exposures to VZV, while the rate of reactivation increases with both the time elapsed since the last re-exposure and the individual's age[134]

- the study for the Netherlands assumed that 51% of those who are latently infected with VZV and come in contact with an infectious case will receive an immunity boost, with the reactivation rate suppressed ten-fold with each boosting event and the reactivation rate increasing with time since the last boosting event.[128]

*Utility values for quality-adjusted life years (QALYs)*

Utility values per health effect, used to calculate QALYs, were directly reported in three reviews.[126, 129, 134] The utility values used in these studies were sourced from different studies and varied for the same health states. A calculated QALY loss per case per health effect was reported in five reviews,[127, 128, 130, 132, 133] with varying reporting of utility values and duration in the health state used to calculate the QALY loss. The final review reported the overall QALY loss per case associated with each vaccination strategy assessed.[131]

### 6.4.7 Economic results

All studies calculated incremental cost-effectiveness ratios (ICERs) and all reported incremental costs per quality-adjusted life year (QALY) gained or saved. The strategies assessed were largely cost-effective from both the payer and societal perspectives, relative to no vaccination, with the following exceptions:

- From the payer's perspective in the UK model, a two-dose quadrivalent strategy (with both GSK and MSD vaccines) was not cost effective over the short-term (20 years) time horizon, with the cost per QALY gained >£20,000. Additionally, the two-dose quadrivalent strategy was not cost effective over the medium-term (40 years) with the MSD vaccine.[132]

- In the study conducted for Italy from the tax payer's perspective, when progressive partial immunity due to exogenous boosting was assumed, routine varicella vaccination was dominated by no vaccination (that is, was more costly and less effective than), in the short and medium terms.[134]

- The study conducted for Alberta, Canada assessed both short and long dose interval strategies and neither were cost effective from the payer's

perspective (ICER>$125,000/QALY gained), versus no vaccination, when exogenous boosting of immunity to herpes zoster was assumed.[126]

- The results from the study conducted from the societal perspective for the Netherlands, suggest that:
    - varicella vaccination is predominantly dominated by no vaccination when exogenous boosting of immunity to herpes zoster is assumed and vaccine VZV reactivation is not assumed
    - varicella vaccination is dominated by no vaccination when exogenous boosting of immunity to herpes zoster is assumed and vaccine VZV reactivation is assumed.[128]

### 6.4.8 Authors' conclusions

While six of the included studies concluded that two-dose varicella vaccination was cost effective or cost saving,[127, 129-133] two of the studies noted that the cost effectiveness of varicella vaccination (from the payer's perspective)[126] is dependent on the impact on incidence of herpes zoster associated with exogenous boosting.[126, 128] A further study concluded that varicella vaccination would negatively impact the overall burden of VZV in the short and the medium term and therefore the introduction of a varicella vaccination strategy on its own would not be considered cost effective from the perspective of the health care payer.[134]

### 6.4.9 Critical appraisal

A critical appraisal of all included studies was undertaken using the framework for quality assessment of decision-analytic models proposed by Philips et al.[125] While overall the appraisal did not raise major concerns with the quality of included studies, within each of three domains there were some concerns. In terms of the 'Structure' domain, there were some concerns with regard to structural assumptions where a number of studies did not consider the impact of waning immunity. Additionally, the base case time horizon in three studies was limited to 50 years which is arguably too short given that VZV reactivation and herpes zoster typically occur after the age of 50. Within the 'Data' domain, there were some concerns with regard to the level of detail provided for some parameter data and the comprehensiveness of the assessment of uncertainty. Lastly, within the 'Consistency' domain, a number of studies did not describe model validation or consistency checks.

## 6.5 Discussion and comparison of results with most recently published systematic review

### 6.5.1 General and model characteristics

This rapid review provides an update of the evidence on economic evaluation studies that model routine childhood varicella vaccination, since the most recently published systematic review (included studies published up until October 2013).[123] Similar to the last systematic review, most of the studies in this review were conducted for European countries, with approximately half of included studies funded by industry.

While 10 of 23 studies in the previous systematic review did not use a fully dynamic modelling approach in terms of simulating the transmission dynamics of varicella, all but one study (Markov model)[130] in the current review were based on dynamic transmission modelling. In the previous review, most of the models were reported to have ignored the relationship between varicella and herpes zoster; however seven of the nine studies in the current review did include the impact of varicella vaccination on incidence of herpes zoster associated with the exogenous boosting theory. The nature of communicable diseases and specifically their transmissibility requires specific consideration when conducting modelling to assess the cost effectiveness of vaccination programmes. VZV has a non-constant force of infection and the probability of infection is related to the number of susceptible, infectious, exposed and recovered individuals in the population, which in turn impacts the future probability of infection. In contrast to non-communicable diseases, an intervention such as vaccination also produces population-level effects, such as herd immunity, potential shifts in the age of infection, and in the case of varicella vaccination, a potential increase in incidence of herpes zoster associated with the exogenous boosting theory.[1, 5, 6] In order to model these interactions and externalities, along with the full range of effects of a vaccination programme, a dynamic transmission model is the most appropriate model to use.[137]

The majority of studies in both reviews conducted the analysis from both the healthcare payer and societal perspectives which is line with recommended good practice guidelines for the economic analysis of vaccination programmes.[137, 138] It is argued that economic evaluations of vaccines should adopt a broader perspective than the healthcare payer perspective and should be conducted from the societal perspective to incorporate their full value; the elements of vaccines that are undervalued when a payer perspective is adopted include the prevention of complications, health gains for care givers, herd effects, community benefits, enhanced productivity and the promotion of equity.[138] In Ireland, the 'reference case' or preferred method in the primary analysis for health technology assessment (HTA) is to adopt the perspective of the publicly funded health and social care

system. However, in circumstances where it may be appropriate to adopt a wider perspective, the guidance also provides for this possibility, but it must be clearly justified and supported by sufficient evidence.(139)

Overall, the time horizon adopted in modelling studies in the earlier review was shorter than that in the current review. Almost half of those in the earlier review adopted a time horizon of 30 years or less, compared with at least 50 years for all studies in the current review. Given the nature of VZV and the potential for reactivation resulting in herpes zoster, typically several decades after primary infection, an economic model incorporating a longer time horizon in the base case analysis is arguably the most appropriate.

### 6.5.2 Intervention and vaccination strategies

Most of the studies in the earlier systematic review considered a one-dose schedule only, while all studies in the present review considered a two-dose schedule only. This difference likely reflects the predominant strategies in place at the time of publication of the original studies in the earlier review, and the subsequent change in strategy in some countries from a one- to a two-dose schedule. While six of the studies in the present review conducted modelling for countries that were also included in the earlier review, it is noted that the present review included studies from Norway, the Netherlands and Sweden, all assessing a two-dose strategy, but no studies assessing a one-dose strategy were identified for these three countries.

The age at first dose vaccination varied more widely in the earlier review, ranging from 12 to 36 months, compared to a range of nine to 15 months in this review. This difference may reflect underlying changes in the composition of childhood vaccination schedules including the timing of the administration of different vaccines between countries. In the earlier review, assumed vaccination coverage rates (for one-dose) ranged from 47% to 97%, with approximately half the studies assuming a coverage rate between 70% and 90%. Assumed coverage rates were higher in studies in the current review, generally ranging from 80% to 95%. Again, these differences may be explained by varying coverage rates in different countries and or increasing coverage rates within countries over time.

### 6.5.3 Vaccine characteristics

The efficacy/effectiveness data used for one-dose varicella vaccination strategies varied greatly, ranging from 80 to 97% in the earlier review to 61.7 to 100% in the current review. Given the timing of the two reviews, these differences may reflect available data at the time that individual economic modelling studies were conducted. Approximately 25% of studies in the earlier review did not consider waning of vaccine-induced immunity. Of those that did, almost half used yearly

waning rates of 3.1%, a number of others used 0.5% and others stated that waning was applied to 15% of the protected vaccinees without quantifying the waning rate per year. A UK study included in the previous review used various waning rates ranging from 0.05% to 6.7%. Waning of immunity was considered and waning rates were reported in five of the nine studies in the present review,[127, 129, 130, 132, 133] where one dose rates varied from 2% to 5.88% per annum. Similar to vaccine efficacy/effectiveness data, differing rates may reflect the available data at the time that individual economic modelling studies were conducted.

### 6.5.4 Costs and effects

Included costs and effects were not detailed in the earlier systematic review so a comparison with the present review is not possible. However, the earlier review did note that some studies included the cost of vaccine wastage which was not reported as an included cost in more recent studies. Overall, the included costs and effects were largely consistent across the nine studies included in this review; however, the costs related to febrile seizure associated with vaccination was not included in four studies,[128-130, 134] a single review included the one-off costs associated with the introduction and co-ordination of the vaccination programme (e.g., campaign, materials, leaflets, printing, variable personnel),[128] and two studies did not include the indirect effect of the impact of varicella vaccination on incidence of herpes zoster associated with exogenous boosting.[131, 133]

### 6.5.5 Authors' conclusions

The earlier systematic review concluded that the cost effectiveness of childhood varicella vaccination, versus no vaccination, was to a large extent dependent on the interaction between varicella and herpes zoster and assumptions around exogenous boosting of immunity to herpes zoster. When no exogenous boosting was assumed, varicella vaccination was considered to be cost effective. However, in four studies the inclusion of the impact on incidence of herpes zoster associated with exogenous boosting produced was associated with higher ICERs (that is, vaccination was less cost effective) with ICERs exceeding willingness-to-pay thresholds when considered from the payer's perspective; these studies did not assess cost effectiveness from the societal perspective. In this updated review, while six of the included studies concluded that two-dose varicella vaccination was cost effective or cost saving,[127, 129-133] three of the nine included studies (conducted from the payer, tax payer and societal perspectives) noted that the cost effectiveness of varicella vaccination is dependent on the impact on incidence of herpes zoster associated with exogenous boosting.[126, 128, 134] Given that the evidence around the existence of exogenous boosting is mixed and therefore the potential and magnitude of the impact of varicella vaccination on herpes zoster is uncertain,[140-142] modelling the cost

effectiveness of varicella vaccination should allow for consideration of this indirect effect.

## 6.6 Conclusion

The objective of this rapid review was to examine the approaches taken to modelling the expected costs and benefits of universal childhood varicella vaccination in high income countries and to use the findings to inform the economic modelling of universal childhood varicella vaccination in Ireland. The review identifies a number of important features to be considered in the economic modelling of childhood varicella vaccination. It also highlight a number of changes in the approach to modelling that have occurred over the last number of years. Dynamic transmission models are used increasingly to accurately model the impact of varicella vaccination on VZV transmission, with the epidemiological model output subsequently used in associated economic models. Additionally, and recognising the potential impact of varicella vaccination on the incidence of herpes zoster associated with exogenous boosting, more recent CEAs have typically considered the impact of this indirect effect. Published CEAs of childhood varicella vaccination have adopted more than one perspective and analyses have been conducted from both the payer and societal perspectives, with the latter used to capture the full value of vaccination. All of the features highlighted above will be considered when developing the de novo economic model of varicella vaccination specific to Ireland.

# 7 Economic evaluation

## Key points

- A dynamic transmission model was developed to model the transmission of varicella zoster virus (VZV) in Ireland and the incidence of varicella and herpes zoster diseases both before and after the introduction of a universal childhood varicella vaccination programme.
- The epidemiological outputs from the dynamic transmission model were subsequently used in an economic model developed to estimate the cost effectiveness and budget impact of a universal childhood varicella vaccination programme compared with no vaccination.
- Three alternative vaccination strategies were analysed:
    - One-dose administered at 12 months
    - Two-dose short interval administered at 12 months and 15 months
    - Two-dose long interval administered at 12 months and five years
- The estimated effectiveness of one- and two-dose vaccination strategies were obtained from an overview of reviews of the clinical effectiveness of varicella vaccination.
- From the payer perspective, the incremental cost-effectiveness ratio (ICER) for a one-dose strategy compared with no vaccination was estimated at €8,712 per quality-adjusted life year (QALY) gained. In the deterministic sensitivity analysis, the one-dose strategy was considered cost effective at a willingness to pay (WTP) threshold of €20,000/QALY gained for all parameters tested.
- Compared with one-dose vaccination, the ICERs for a two-dose long interval and two-dose short interval strategy were estimated at €45,090 and €44,106 per QALY gained, respectively. The sensitivity analysis highlighted the uncertainty associated with both ICERs and their cost-effectiveness at a WTP threshold of €45,000/QALY gained.
- The results of the univariate sensitivity analysis demonstrated that the cost-effectiveness results for the one-dose strategy, relative to no vaccination, were most sensitive to changes in the uptake rate and the cost of the vaccine. Similarly, the results of two-dose cost-effectiveness, relative to one-dose, were most sensitive to changes in the uptake rate, the cost of the vaccine and the

QALY loss associated with varicella. When comparing the two-dose strategies, the cost-effectiveness of the two-dose short interval strategy was most sensitive to changes in waning immunity associated with one dose and the force of infection in vaccinated individuals. Given the uncertainty around the cost of the vaccine and the cost of administering it, scenario analyses highlighted the sensitivity of the ICERs to parameter values greater than 20% above base case values.

- From a societal perspective, all three vaccination strategies dominated the no vaccination scenario, being less costly and more effective, with the two-dose short interval strategy dominant over all others.
- The budget impact over five years was estimated at €13.1 million, €28.1 million and €16.1 million for the one-dose, two-dose short interval, and two-dose long interval strategies, respectively. This assumes an annual eligible cohort of 60,000 children per annum. The lower budget impact for the two-dose long interval strategy reflects the fact that only one birth cohort would complete the two-dose schedule within the five year time horizon of the BIA.
- The incremental costs associated with the introduction of a varicella vaccination programme include associated cost savings, mainly comprising the costs associated with a reduction in hospitalisation for varicella. The five-year budget impact was most sensitive to changes in the cost of the vaccine.
- This modelling study is subject to a number of limitations. As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values:
    - There are a number of aspects of the epidemiology of VZV infection that are not fully understood and therefore key model parameters, including the duration of cell-mediated immunity following primary VZV infection, are highly uncertain. Additionally, the exogenous boosting theory is poorly understood, much debated and the magnitude of the effect, if it exists, is unknown.
    - While probabilistic sensitivity analysis (PSA) is the preferred approach for exploring uncertainty arising from parameter imprecision, a full PSA was not possible due to the complexity of the model which created a significant computational burden.

## 7.1 Introduction

This chapter firstly describes the development of an epidemiological model of varicella and herpes zoster infection for Ireland. The chapter then describes the economic evaluation, comprising cost-utility and budget impact analyses, to estimate the costs and benefits associated with the expansion of the childhood immunisation schedule to include varicella vaccination.

## 7.2 Development of the Epidemiological Model

### 7.2.1 Objective

An epidemiological model of varicella and herpes zoster was developed to characterise the incidence of both diseases in Ireland without varicella vaccination. The model was used to assess the impact of the introduction of routine childhood varicella vaccination on disease incidence, and to obtain health state outputs for use in the economic evaluation of a routine childhood varicella vaccination programme.

### 7.2.1 Model overview

When conducting modelling for economic evaluation of communicable diseases, the transmissible nature of these diseases is what distinguishes them from other diseases. VZV has a non-constant force of infection which is dependent on the number of infectious individuals in the population, contact patterns between individuals, and the probability of infection given contact with an infectious person. In contrast to non-communicable diseases, an intervention such as vaccination also produces population-level effects, in addition to benefits for those who are directly reached by a vaccination program. In order to model the full range of effects of a varicella vaccination programme, including herd immunity, potential shifts in the age of infection, and potential for waning of vaccine protection, a dynamic transmission model was deemed to be the most appropriate.

A deterministic, age-structured dynamic transmission model of varicella and herpes zoster was developed for Ireland using a hypothetical patient cohort. The model structure was informed by a review of economic models published for high income countries (Chapter 6) and largely adapted from models developed for France,[127] and the UK.[132] The model, developed in R® (version 4.1.2), describes the transmission of the varicella zoster virus (VZV), the incidence of varicella and herpes zoster diseases over 80 years and the impact of the introduction of one-dose and two-dose varicella vaccination. The model was built using Irish demographic data and epidemiological data of varicella and herpes zoster diseases sourced from the Health Protection Surveillance Centre (HPSC) and the academic literature.[2, 45, 143, 144]

Age-specific contact data from the UK subset of the POLYMOD were used to characterise the spread of VZV to cause varicella.[145]

### 7.2.2 Population

A population of approximately five million people was stratified into 16 age cohorts, based on the current population distribution in Ireland,[2] as follows:

- a one-year age group from birth to 11 months inclusive
- a three-month age group from 12 to 14 months inclusive
- a nine-month age group from 15 to 23 months inclusive
- three one-year age groups from two to four years inclusive
- three five-year age groups from five to 19 years inclusive
- six ten-year age groups from 20 to 79 years inclusive and
- a single age group from and including 80 years.

The one year old age group was split as described above to model a proposed two-dose regimen where the first dose is administered at 12 months and the second dose is administered at 15 months. The ageing process was reflected in the model where births, ageing and death occurred continuously. The last age cohort (≥80 years) was absorptive, with no ageing from the group. The model assumed that the annual number of births and all-cause mortality rates in each age cohort were constant over time (based on 2020 rates in Ireland).[2]

### 7.2.3 Model structure

The epidemiological model is a mathematical representation, using a system of differential equations, of VZV transmission and the occurrence of varicella and herpes zoster diseases with and without varicella vaccination. A simplified model structure is presented in Figure 7.1, illustrating a number of distinct epidemiological states (mutually exclusive compartments) and the movement of individuals (arrows) through the states.

### 7.2.4 Model flows

Individuals follow a pathway of either natural varicella progression or, following the introduction of a varicella vaccination programme, vaccination followed by breakthrough varicella. Natural varicella progression comprises four varicella disease states (susceptible, latent, infectious and recovered) followed by three herpes zoster

disease states (susceptible, infected and recovered). While an individual who has shingles can pass VZV to those susceptible to chickenpox (through direct contact with the fluid from rash blisters), the risk is considered low and therefore was not included in the model.[146] The vaccination followed by breakthrough varicella pathway comprises four varicella vaccination states where individuals are either fully protected (one-dose protected or two-dose protected), partially protected (vaccinated but susceptible) or, where there is vaccine failure, susceptible. The same pathway includes a further six states for vaccinated individuals who remain susceptible to breakthrough varicella and herpes zoster. Although not presented in Figure 1, ageing and mortality are continuous in the model. A detailed description of the model flows is provided below and the differential equations for each age group are provided in Appendix A7.1.

#### 7.2.4.1 Natural varicella disease pathway

Individuals are born into the model at a rate equal to the birth rate, $b$. It was assumed that those born into the model have maternally acquired protection against VZV infection lasting for six months from birth. Susceptible individuals (S) become infected with varicella, and move to the latent state (E) at a rate given by the age-dependent force of infection, $\lambda(a)$. The rate of movement from E to the infectious state (I) is given by the duration of the latent period for varicella, $\sigma$. The rate of movement from I to the recovered state (R) is given by duration of the infectious period for varicella, $\gamma_V$.

Following recovery from varicella, individuals gain lifelong immunity to varicella, but became susceptible to herpes zoster. The rate of movement from R to the susceptible to herpes zoster state ($S_Z$) is given by the duration of cell-mediated immunity, $\delta$. Once in $S_z$, individuals develop herpes zoster and move to the infected zoster state ($I_z$) at a rate given by an age-dependent reactivation rate, $\rho(a)$. The rate of movement from $I_z$ to the recovered zoster state ($R_z$) is given by duration of zoster infection, $\gamma_z$. Following herpes zoster infection, individuals become permanently immune to herpes zoster and remained in $R_z$.

Under the exogenous boosting theory (examined in a scenario analysis), individuals in $S_z$ state who are exposed to the VZV gain a boost to their cell-mediated immunity and they temporarily move from $S_z$ back to $R_v$ at a rate given by, $g(a)\lambda(a)$.

#### 7.2.4.2 Varicella vaccination pathway

Three vaccination strategies were tested in the model:

- One-dose - vaccine administered at 12 months

- Two-dose short interval - vaccines administered at 12 months and 15 months
- Two-dose long interval - vaccines administered at 12 months and five years

#### 7.2.4.2.1 Varicella vaccination pathway – one dose

The model assumed that individuals are offered the first vaccine dose at the point at which they age into the age group at which the first dose is offered. Following the first vaccine dose:

- A proportion of individuals remain susceptible to varicella following vaccine failure, *vf1*. These individuals move from S to the vaccine failure susceptible state (FVS) and become infected with varicella at the same age-dependent force of infection rate as susceptible individuals who are not vaccinated, $\lambda(a)$.
- Among those who seroconvert after the first dose, *1-vf1*, a proportion of individuals, corresponding to the first dose vaccine effectiveness, *ve1*, is protected and moves from S to the vaccinated 1-dose protected state (V1P). The remaining proportion, *1-ve1*, is partially protected but remains susceptible and moves from S to the vaccinated susceptible state (VS).

#### 7.2.4.2.2 Varicella vaccination pathway – two doses

The model assumed that individuals are offered the second vaccine dose at the point at which they age into the age group at which the second dose is offered. Following the second vaccine dose:

- Individuals in V1P, excluding a proportion for whom the second dose failed, vf2, move from V1P to the vaccinated 2-dose protected state (V2P).
- Among individuals who received the first dose but remain susceptible, VS, a proportion of individuals, excluding those for whom the second dose failed, *vf2*, acquire protection corresponding to the second dose vaccine effectiveness, *ve2*, and move to V2P. The remaining proportion, *1-ve2*, stay in VS.
- Among those who experience vaccine failure with the first dose, VFS, a proportion of individuals, excluding those for whom the second dose also failed, acquire one-dose protection corresponding to one-dose vaccine effectiveness, and move from VFS to the 1-dose protected after first dose vaccine failure state (V1Q). The remaining proportion, *1-ve1*, is partially protected but remains susceptible and moves from the VFS state to VS. Those for whom both the first and second doses fail and who do not seroconvert,

remain in VFS and become infected with varicella at the same age-dependent force of infection rate as susceptible individuals who are not vaccinated, $\lambda(a)$.

#### 7.2.4.3 Waning immunity following vaccination

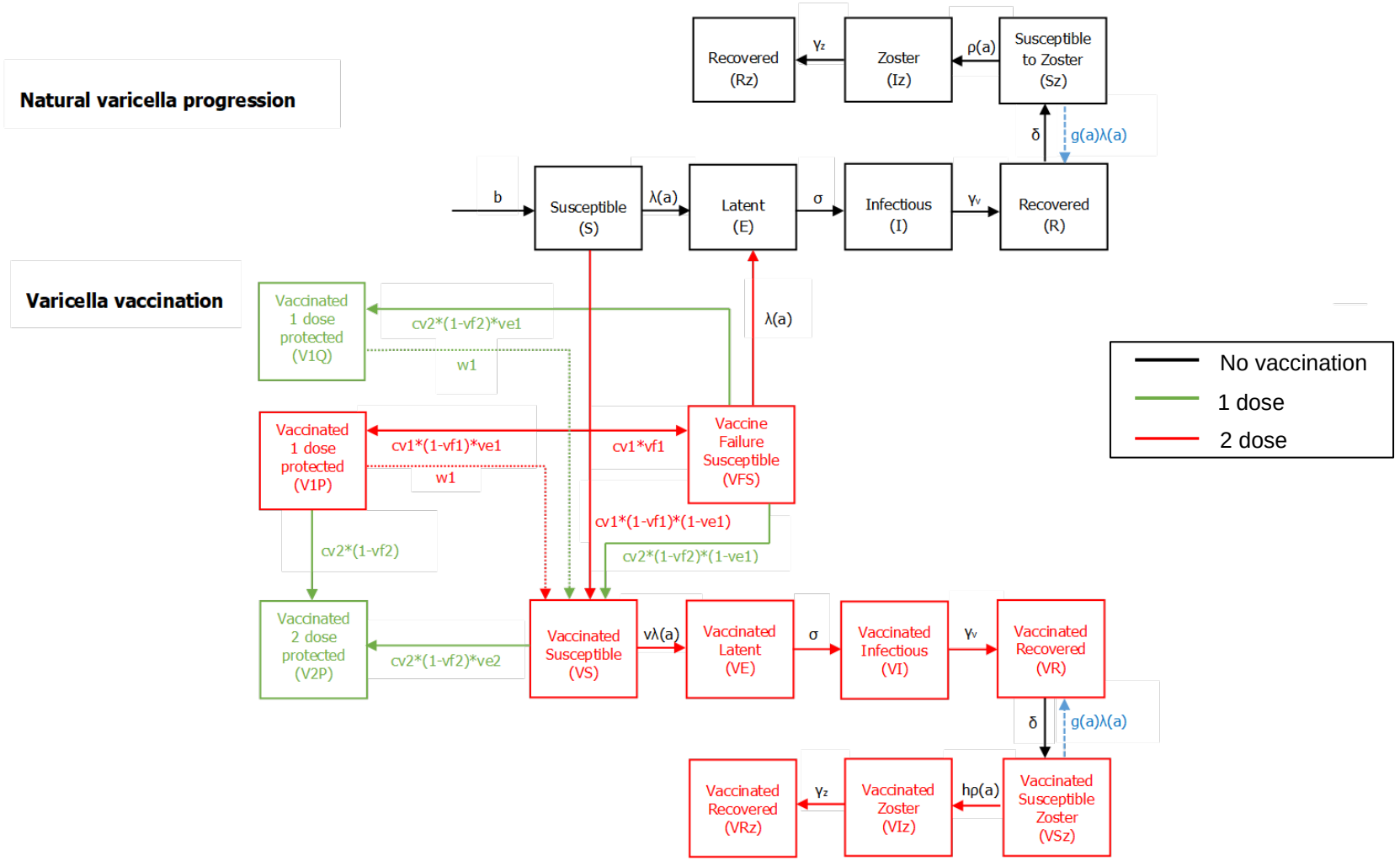
The protection conferred by one dose of the vaccine is assumed to wane with time while two doses are assumed to confer permanent immunity. Therefore, those who are protected with one dose (V1P) are again susceptible to VZV over time and move to VS at a rate given by $w1$. It was assumed that those in the VS state can be infected with breakthrough varicella and move to the vaccinated latent state (VE) at an age-dependent force of infection rate, $h\lambda(a)$, that is lower than that for wild type varicella, $\lambda(a)$. The rate of movement of individuals from VE to the vaccinated infectious state (VI) is given by the duration of the latent period, $\sigma$. The rate of movement of individuals from VI to the vaccinated recovered state (VR) is given by the duration of the infectious period with breakthrough varicella, $\gamma_v$.

Following recovery from breakthrough varicella, individuals gain lifelong immunity to varicella, but become susceptible to herpes zoster. The rate of movement from the vaccinated recovered state (VR) to the vaccinated susceptible to zoster state ($VS_Z$) is given by the duration of cell-mediated immunity, $\delta$. Once in $VS_z$, individuals develop herpes zoster and move to the vaccinated zoster state ($VI_z$) at a rate given by an age-dependent reactivation rate, $h\rho(a)$. The rate of movement from $VI_z$ to the vaccinated recovered zoster state ($VR_z$) is given by the duration of the infectious period with zoster, $\gamma_z$. Following herpes zoster infection, it is assumed that individuals become permanently immune to herpes zoster and remain in $VR_z$.

Under the exogenous boosting theory (examined in a scenario analysis), individuals in $S_z$ state who are exposed to the VZV, gain a boost to their cell-mediated immunity and they temporarily move from $S_z$ back to $R_v$ at a rate given by, $g(a)\lambda(a)$.

## Figure 7.1 Model structure

Natural progression of varicella + vaccination



### 7.2.5 Initial model states

To initialise and stabilise the model, it was first run for 80 years. The state values at year 80 were then used as the starting values for the base case model. The base case model assumed no exogenous boosting and was run over an 80 year time horizon, with the output used in the economic evaluation. For each age group, the number of infectious individuals on day one was estimated from varicella incidence data sourced from a systematic review of seroprevalence data in European countries.[45] The number of individuals in the latent state was estimated based on a reproduction number of 10 and an infectious period of seven days. The number of individuals recovered from varicella infection at the outset of the model was estimated based on the seroprevalence data described above,[45] and was subsequently adjusted to account for the progression of individuals to being susceptible to VZV reactivation and the development of herpes zoster (see below). The remaining individuals in each age group, with the exception of the first age group, were classified as susceptible to VZV. It was assumed that approximately 50% of those aged 0-12 months were not susceptible to VZV due to maternal acquired immunity, which was assumed, on average, to last for six months from birth.[147, 148]

With regard to the herpes zoster disease states, the number of infected individuals was estimated by applying a smoothing function, using a generalised additive model, to Irish incidence data (2015 to 2019 inclusive) provided by the HPSC.[143] The smoothed herpes zoster incidence by age group was then used for calibration to determine the VZV reactivation rates. The number of individuals recovered from herpes zoster was calculated based on estimated prevalence rates using the incidence data above. An adjustment to the number of individuals recovered from varicella (described above) was required recognising the progression of individuals to being susceptible to VZV reactivation. This adjustment was calculated based on an average duration of cell mediated immunity of two years following recovering from varicella. Following the adjustment to the numbers recovered from varicella, the remaining individuals in the age cohort were considered susceptible to VZV reactivation.

### 7.2.6 Contact matrix

The risk of VZV infection to cause varicella, or the force of infection, is a function of the number of infected people in the population, the average number of contacts per unit of time, and the probability of infection given contact. Daily contact data from the UK subset of the POLYMOD dataset were used to characterise the spread of VZV to cause varicella.[145] The UK matrix, which includes home, work, school, leisure,

transport and other contact rates, was adjusted to align with the age groups specified in our epidemiological model. Additionally, given that the one year old age group is split in our model, a number of further adjustments were made to the contact matrix. Assuming a uniform age distribution within the single year of age, the one year old age group were split into 12 to 14 months and 15 to 23 months age groups respectively using the ratio of 1:3. The numbers of contacts between these and other age groups were allocated pro-rata. It was ensured that the sum of the total number of contacts for the two one year old age subgroups was approximately equal to the total number of contacts for the one year old age group. The contact matrix is provided in Appendix A7.2.

### 7.2.7 Model input parameters

Model input parameters, both biological and vaccine related, are provided in Tables 7.1 and 7.2, respectively.

### 7.2.8 Model output

The model was run in one-day intervals over 80 year time horizon. The model output provided the number of individuals in each age group for both the varicella and herpes zoster infectious disease states, with and without vaccination, for each day over the time period.

### 7.2.9 Assessment and quantification of uncertainty

The complexity of the model and need to incorporate sixteen age bands created a significant computational burden. For this reason, a full probabilistic analysis was not feasible. To enable an assessment of uncertainty, deterministic sensitivity analyses (DSA) were conducted to test the impact of parameter uncertainty and the robustness of the epidemiological model outputs.

#### 7.2.9.1 Sensitivity analysis

Parameter uncertainty was assessed using univariate sensitivity analysis. Specific parameter values were fixed in turn at lower and upper 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.

#### 7.2.9.2 Scenario analysis

Scenario analysis was conducted to assess structural uncertainty in the model with regard to the base case assumption that there was no exogenous boosting.

### 7.2.10 Model validation and calibration

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

## Table 7.1 Biological input parameters

| Parameter | Parameter name | Parameter description | Parameter values | Source |
|---|---|---|---|---|
| α | Ageing rate | Assumed continuous with ageing from all age groups except ≥80years age group and ageing to all age groups except 0-11months age group. | Age group 1: 1.00<br>Age group 2: 4.01<br>Age group 3: 1.33<br>Age groups 4-6: 1.00<br>Age groups 7-9: 0.20<br>Age groups 10-15: 1.00 | Rates applied according to the number of yearly ages within each age group. |
| b | Birth rate | Assumed continuous and constant into the first age group | 1.1879%<br>(assumes a notional birth cohort of 55,500 per year) | CSO[2] |
| μ | All-cause mortality rate | All-cause mortality rate (by age group) | Age group 1: 0.3244%<br>Age groups 2-6: 0.0056%<br>Age groups 7-8: 0.0051%<br>Age group 9: 0.0230%<br>Age group 10: 0.0430%<br>Age group 11: 0.0867%<br>Age group 12: 0.2102%<br>Age group 13: 0.5283%<br>Age group 14: 1.3808%<br>Age group 15: 4.1994%<br>Age group 16: 13.7546% | CSO[2] |
| λ(a) | Force of VZV infection | Force of VZV infection (by age group),<br>where λ = β * (I+VI)/N, and β = c*p<br>β = varicella infection rate<br>I = number of infectious people<br>VI = number of infectious people in those vaccinated (breakthrough)<br>N = total number of people | Ongoing calculation for each age group | Calculation within model |
| | | c = average number of contacts a susceptible person makes per day | Appendix A7.2 | Contact matrix[145] |
| | | p = the probability of a susceptible person becoming infected with varicella given contact with an infectious person | 0.12 | Calibration |
| σ | Incubation rate for varicella | Average duration of varicella incubation = 1/σ | 14 days | [149] |
| $\gamma_v$ | Recovery rate from varicella | Average duration of varicella infection = 1/$\gamma_v$ | 7 days | [149] |
| δ | Waning rate from recovered varicella to susceptible to HZ | Average duration of cell-mediated immunity following varicella = 1/δ | 2 years | [132] |
| g(a)λ(a) | Exogenous boosting against HZ | Rate of exogenous boosting against HZ (by age group) | 100% for all age groups<br>[Explored in a scenario analysis] | Assumption |
| ρ(a) | Reactivation rate of infectious HZ | Reactivation rate of infectious HZ (by age group) | Age group 1: 2.5600%<br>Age group 2: 1.3730%<br>Age group 3: 0.4462%<br>Age group 4: 0.2560%<br>Age group 5: 0.1860%<br>Age group 6: 0.1540%<br>Age group 7: 0.1192%<br>Age group 8: 0.1272%<br>Age group 9: 0.1292%<br>Age group 10: 0.1501%<br>Age group 11: 0.1772%<br>Age group 12: 0.2379%<br>Age group 13: 0.4869%<br>Age group 14: 0.8417%<br>Age group 15: 1.5616%<br>Age group 16: 3.9661% | Calibration |

| Parameter | Parameter name | Parameter description | Parameter values | Source |
|---|---|---|---|---|
| $\gamma_z$ | Recovery rate from HZ | Average duration of HZ infection = $1/\gamma_z$ | 7 days | (149) |
| $v\lambda(a)$ | Force of VZV infection in those vaccinated | Force of VZV infection to cause breakthrough varicella (by age group) | 0.73 * λ(a)<br>[Lower bound 0.5, Upper bound 1.0] | (149) |
| h | Relative VZV reactivation after vaccination | Reactivation rate of infectious HZ following breakthrough varicella | 0.167 | (150) |

**Key:** CSO – Central Statistics Office; HZ – herpes zoster; VZV – varicella zoster virus

## Table 7.2 Vaccination input parameters

| Parameter | Parameter name | Parameter description | Mean parameter values | Lower bound parameter values | Upper bound parameter values | Source |
|---|---|---|---|---|---|---|
| cv1 | Coverage rate 1-dose strategy | Vaccination coverage rate for 1-dose strategy | 88% | 70% | 93% | Assumed based on uptake rates for existing childhood immunisation programmes in Ireland(151, 152) |
| cv2 | Coverage rate 2-dose strategy | Vaccination coverage rate for 2-dose strategy | 88% | 70% | 93% | |
| vf1 | Vaccine failure 1st dose | Probability of complete vaccine failure after 1st dose | 5% | - | - | (153) |
| vf2 | Vaccine failure 2nd dose | Probability of complete vaccine failure after 2nd dose | 5% | - | - | (153) |
| ve1 | Vaccine efficacy 1st dose | Efficacy of 1st vaccine dose | 74% | 64% | 85% | (154) |
| ve2 | Vaccine efficacy 2nd dose | Efficacy of 2nd vaccine dose<br>(% of individuals unprotected after 1st dose who are protected after 2nd dose) | 67%<br>(2-dose VE = 91%) | 57%<br>(2-dose VE = 85%) | 75%<br>(2-dose VE = 95%) | (154) |
| w1 | Waning rate 1-dose | Waning rate following one dose | 4% p.a. | 2% p.a. | 6%p.a. | (155) |

**Key:** p.a. per annum; VE – vaccine effectiveness

## 7.3 Economic Evaluation

### 7.3.1 Methods

The economic evaluation was conducted in line with national HTA guidelines,[139] reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement,[156] and undertaken in R Studio[157] and Microsoft Excel 2013.[158]

#### 7.3.1.1 Study objective

The purpose of the health economic evaluation was to estimate the cost effectiveness and budget impact of universal childhood varicella vaccination in Ireland. The cost-utility analysis (CUA) estimates the costs and outcomes of alternative vaccination strategies, while the budget impact analysis (BIA) provides a means of predicting the potential financial impact of introducing a childhood varicella vaccination programme.

#### 7.3.1.2 Target population

Varicella is a common, acute and highly contagious disease, affecting in excess of 50,000 people, mainly children, in Ireland each year. The epidemiology of varicella in children is described in full in Chapter 3. The target population for the childhood varicella vaccination programme is all children aged 1 year. For the model, the target population comprised an annual notional cohort of approximately 55,500 children aged 12 months.

#### 7.3.1.3 Technology

The technology being assessed is a sole primary care-based, or primary care- and schools-based varicella vaccination programme, depending on the vaccination strategy (see section 7.3.2). The aim of the technology is to reduce VZV infection in children and thereby reduce varicella disease. A detailed description of the technology is provided in chapter 2.

#### 7.3.1.4 Comparator

Three alternative vaccination strategies were assessed in both the CUA and BIA. The full set of included strategies was:

- No vaccination
- One-dose vaccination given at 12 months of age

- Two-dose vaccination given at 12 and 15 months of age
- Two-dose vaccination given at 12 months and five years of age.

#### 7.3.1.5 Study design

A CUA was undertaken to estimate the incremental cost and health benefits associated with competing alternative varicella vaccination strategies. 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 CUA was undertaken using the outputs from the epidemiological model previously described and simulated the long-term costs and patient outcomes associated with varicella and herpes zoster.

The BIA estimated the incremental cost to the Health Service Executive (HSE) of implementing a universal childhood varicella vaccination programme over a five-year time horizon.

#### 7.3.1.6 Economic model structure

The dynamic transmission model described above estimated the incidence of varicella and herpes zoster disease in a hypothetical population cohort divided into 16 age groups, with and without varicella vaccination. The disease state outputs relating to incidence of disease (numbers infected with varicella and herpes zoster) were subsequently used in the economic model that was developed in MS Excel.

In the absence of varicella vaccination, it was assumed that those infected with varicella could develop severe varicella requiring hospitalisation and those infected with herpes zoster could develop severe herpes zoster, requiring hospitalisation, and post herpetic neuralgia. When varicella vaccination is introduced, it was assumed the same possible outcomes as above for non-vaccinated individuals and assumed individuals who are vaccinated against varicella could develop breakthrough varicella and herpes zoster. In line with the findings from the overview of reviews of the safety of varicella vaccination (chapter 5), it was also assumed that non-serious adverse events were a possible outcome following vaccination. Costs and QALY losses were assigned to each of the health outcomes for both the no vaccination and vaccination scenarios, enabling the calculation of the incremental costs and incremental QALYs associated with vaccination.

Similarly, in the absence of vaccination, the BIA model assumed that those infected with varicella could develop severe varicella requiring hospitalisation and those infected with herpes zoster could develop severe herpes zoster, requiring hospitalisation, and post herpetic neuralgia. When varicella vaccination is introduced,

the model assumed the same possible outcomes as above for non-vaccinated individuals and assumed individuals who are vaccinated against varicella could develop breakthrough varicella and herpes zoster. Costs were assigned to these health outcomes for both the no vaccination and vaccination scenarios. This enabled the calculation of the costs averted as a result of vaccination.

#### 7.3.1.7 Perspective, time horizon and discounting

The CUA adopted the perspective of both the Irish publicly-funded health and social care system, 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.[137] 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 diseases and time required to care for those with the diseases, 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 an 80 year time horizon, and discounted at a rate of 4% as specified in national guidelines.[139] Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future.

In the BIA, the incremental costs associated with introducing a varicella 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,[159] no discounting was applied.

#### 7.3.1.8 Model input parameters

Probabilities, costs and QALY losses were estimated from a variety of published sources, national datasets for Ireland and international datasets, including those published by the Central Statistics Office (CSO), the Healthcare Pricing Office (for Hospital In-Patient Enquiry (HIPE) data), the Health Protection Surveillance Centre and Eurostat.

Model inputs were selected with consideration to the hierarchy of evidence, as well as generalisability to the Irish context. All economic model input parameters are provided in Appendix A7.3.

Inputs for the BIA 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 analysis.

#### 7.3.1.8.1 Health outcomes - varicella

The total number of individuals infected with varicella (by age group and year) was obtained from the epidemiological model output. It was assumed that a portion of individuals with varicella develop severe varicella, requiring hospitalisation. The probability of severe varicella was estimated from HIPE discharge data for years 2015 to 2019 inclusive (Table 7.3). These data included the total number of inpatient and day case discharges with a primary diagnosis of B01X Varicella [chickenpox] by age group and year.

Infectious disease models display peaks and troughs in incidence to reflect the changing balance of susceptible and recovered individuals. The timing of those peaks and troughs are a function of when and how vaccination is implemented. A curve was fitted to estimate the trend in mean incidence of varicella over time to reflect the 'on average' impact of vaccination in incidence over the five year time frame of the BIA. The mean incidence was then used to estimate the costs associated with varicella incidence in terms of GP care, medication and hospitalisation.

#### 7.3.1.8.2 Health outcomes – herpes zoster

The total number of individuals infected with herpes zoster (by age group and year) was obtained from the epidemiological model output. It was assumed that a portion of individuals with acute herpes zoster develop severe herpes zoster, requiring hospitalisation. The probability of severe herpes zoster, requiring hospitalisation, was estimated from HIPE discharge data for years 2015 to 2019 inclusive (Table 7.4). These data included the total number of inpatient and day case discharges with a primary diagnosis of B02X Zoster [herpes zoster] by age group and year. It was also assumed that a portion of individuals with acute herpes zoster develop post herpetic neuralgia. The probability of developing post herpetic neuralgia (by age) was obtained from the literature,[160] with rates consistent with the overall rate assumed in a recent Irish study.[161, 162]

**Table 7.3 Estimated probability of hospitalisation for varicella**

| Age group | Estimated probability of hospitalisation for |
|---|---|
| <1 year | 1.17% |
| 1 year | 0.22% |
| 2 years | 0.42% |
| 3 years | 0.41% |
| 4 years | 0.41% |
| 5 to 9 years | 0.51% |
| 10 to 19 | 0.26% |
| 20 to 39 | 0.79% |
| 40 to 59 | 2.80% |
| 60 to 79 | 12.67% |
| ≥80 years | 100.00% |

**Table 7.4 Estimated probability of hospitalisation for herpes zoster**

| Age group | Estimated probability of hospitalisation for herpes zoster[163] |
|---|---|
| 0 to 9 years | 6.02% |
| 10 to 19 years | 2.96% |
| 20 to 29 years | 1.45% |
| 30 to 39 years | 2.09% |
| 40 to 49 years | 1.64% |
| 49 to 59 years | 1.21% |
| 60 to 69 years | 1.56% |
| 70 to 79 years | 1.45% |
| ≥80 years | 0.84% |

#### 7.3.1.8.3 Health outcomes – safety of varicella vaccination

The assessment of the safety of varicella vaccination (chapter 5) showed that overall the evidence suggests that varicella vaccination is safe and while mild local and systemic reactions are relatively common, serious adverse events are rare. For the purpose of the CUA it was assumed that 27% of all varicella vaccinations result in mild adverse events that result in a QALY loss, but do not require medical intervention.[164] Serious adverse events were not included in the model.

#### 7.3.1.8.4 Utility and QALY losses

Utility is a measure of perceived health-related quality of life (HR-QoL) in a given health/disease state, with improvements or reductions in HRQoL translating into utility increments or decrements, respectively. Typically, values range from one (that is, full health) to zero (that is, death). QALY losses are calculated based on the utility loss associated with being in a disease state (compared with full health) and the average duration of being in that disease state. The studies included in the rapid review of economic modelling studies of varicella vaccination (Chapter 6) largely reported average QALY losses (rather than utility values) associated with varicella and breakthrough varicella that were sourced from the literature. The QALY losses for children were derived from a UK study where parents of children with prior history of varicella were asked to rate the health state of a child with varicella using a generic health preference-based instrument (Health Utilities Index Mark 2 [HUI2]), while the QALY loss for adults was assumed to be the same as that for mild herpes zoster.[165] Average QALY losses associated with herpes zoster and post herpetic neuralgia were sourced from the literature.[166] Base case QALY losses for varicella and herpes zoster disease states are provided in Table 7.5. The QALY loss associated with mild adverse events following varicella vaccination were not reported in any of the studies reviewed for Chapter 6. Their non-inclusion may possibly be because the impact on health-related quality of life is so small as to not be measureable. For the purpose of the CUA, a QALY loss of 0.0001 was assumed. Based on a utility loss for one day, this equates to an annual utility decrement of

0.0365 which is similar with the base case value used in a previous HTA of HPV vaccination for boys.[167]

### Table 7.5 QALY losses for disease states

| | Age groups | | | | | |
|---|---|---|---|---|---|---|
| **Disease state** | **0-4yrs** | **5-14yrs** | **15-44yrs** | **45-64yrs** | **≥65yrs** | **Source** |
| Varicella | 0.0040 | 0.0040 | 0.0050 | 0.0050 | 0.0050 | [165] |
| **Disease state** | **All** | | | | | **Source** |
| Breakthrough varicella | 0.001 | | | | | [165] |
| **Disease state** | **0-69yrs** | | **≥70yrs** | | | **Source** |
| Herpes zoster | 0.0100 | | 0.0120 | | | [166] |
| Post herpetic neuralgia | 0.1060 | | 0.1560 | | | [166] |

Note: The QALY losses represent the average absolute loss for being in that health state.

#### 7.3.1.8.5 Cost inputs

In accordance with national HTA guidelines, all costs are presented in 2022 Irish Euro (€).[139]

##### 7.3.1.8.5.1 Payer perspective

In the CUA, the costs associated with varicella included the opportunity cost of a GP visit for those with a GP visit or medical card, and the cost of hospitalisation. The probability of attending a GP for varicella was estimated based on age-specific GP consultation rates for varicella from 2015 to 2019, provided by the HPSC (based on surveillance data from sentinel GP practices). In line with the HSE visit card scheme eligibility, it was assumed that all of those in the model age groups up to but excluding the 5-9 year old group and those in the age groups from 70 years upwards, attend with a GP visit card.[168, 169] It is acknowledged that the estimated numbers eligible for a GP visit card in the 5-9 year age group may be underestimated and those eligible in the 70-79 year old age group overestimated given that the GP visit card scheme applies to five year olds but does not apply to 70 year olds. For all other age groups, the probability that those attending the GP have GP visit or medical card was estimated based on eligibility data, as at February 2023, published by the HSE (Table 7.6).[170] The opportunity cost of a GP visit using a GP visit or medical card was sourced from the literature,[171] inflated to 2022 Irish € (using the *Doctor's fees* sub index of the CSO's Consumer Price Index [CPI] monthly series data)[172] and estimated at €49.72.

## Table 7.6 Estimated proportion of the population eligible for a GP visit card and or with a medical card

| Age group | Proportion of population eligible for a GP visit card or with a medical card[170] | Proportion of population with a medical card[170] |
|---|---|---|
| 0-11 months | 100% | 20.8% |
| 12-14 months | 100% | 20.8% |
| 15-23 months | 100% | 20.8% |
| 24-35 months | 100% | 20.8% |
| 36-47 months | 100% | 20.8% |
| 48-59 months | 100% | 20.8% |
| 5 to 9 years | 46.1% | 31.9% |
| 10 to 14 years | 43.8% | 34.4% |
| 15 to 19 years | 24.8% | 21.3% |
| 20 to 29 years | 22.8% | 20.3% |
| 30 to 39 years | 22.8% | 20.5% |
| 40 to 49 years | 27.4% | 24.5% |
| 50 to 59 years | 32.5% | 29.8% |
| 60 to 69 years | 39.2% | 36.6% |
| 70 to 79 years | 100% | 72.4% |
| ≥80 years | 100% | 82.7% |

The average hospitalisation cost for a case of severe varicella, by age group, (Table 7.7) was estimated based on the total number of HIPE discharges with a primary diagnosis of varicella (section 7.3.6.1). Discharge data were split into the following two most common Diagnostic Related Groups (DRGs) for a varicella diagnosis:

- T63A Viral Illness, Major Complexity
- T63B Viral Illness, Minor Complexity.

Discharges with a primary varicella diagnosis not classified as either T63A or T63B, were classified as 'Other'.

Discharge data were reported by age, length of stay, and the associated DRG prices as published by the HPO.[173] The estimated DRG price for those discharges classified as 'Other' was calculated as a weighted average of the other two DRG prices. The costs provided in Table 7.7 are estimated average costs and individual cases could incur higher or lower costs depending on the intensity of treatment and length of stay.

## Table 7.7 Estimated average hospitalisation cost for a case of severe varicella

| Age group | Estimated average hospitalisation cost for a case of severe varicella[163, 173] |
|---|---|
| <1 year | €3,524 |
| 1 year | €3,827 |
| 2 years | €4,136 |
| 3 years | €4,239 |
| 4 years | €4,192 |
| 5 to 9 years | €4,057 |

| Age group | Estimated average hospitalisation cost for a case of severe varicella[163, 173] |
|---|---|
| 10 to 19 years | €3,797 |
| 20 to 39 years | €4,451 |
| 40 to 59 years | €5,484 |
| 60 to 79 years | €7,714 |
| ≥80 years | €7,455 |

For the payer perspective, the costs associated with herpes zoster and post herpetic neuralgia included the opportunity cost of a GP visit for those with a GP visit or medical card, the cost of medication provided to those with medical cards and the cost of hospitalisation for severe herpes zoster. It was assumed that all individuals with herpes zoster and post herpetic neuralgia attend their GP and that all are prescribed medication. The proportion of individuals with a GP visit card or medical card was estimated as described above for varicella (Table 7.5). The opportunity cost associated with a GP visit and prescription medication for herpes zoster and post herpetic neuralgia for a single case was sourced from the literature,[161] and inflated to 2022 Irish € (using the *Doctor's fees* sub index and *Prescribed drugs* sub index of the CSO's Consumer Price Index [CPI] monthly series data);[172] the mean GP cost per case was estimated at €88.18 and €94.23 for acute herpes zoster and post herpetic neuralgia, respectively. The mean prescription medication cost per case was estimated at €104.62 and €101.88 for acute herpes zoster and post herpetic neuralgia, respectively.

The average hospitalisation cost for a case of severe herpes zoster, by age group, (Table 7.8) was estimated based on the total number of HIPE discharges with a primary diagnosis of herpes zoster (section 7.3.6.2). Discharge data were split into the following three most common DRGs for a herpes zoster diagnosis:

- B72B Nervous System Infection Except Viral Meningitis, Minor Complexity
- C60B Acute and Major Eye Infections, Minor Complexity
- J68A Major Skin Disorders, Major Complexity, and

Discharges with a primary herpes zoster diagnosis not classified as B72B, C60B or J68A, were classified as 'Other'.

Discharge data were reported by age group, length of stay, and the associated DRG prices as published by the HPO.[173] 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 7.8 are estimated average costs and individual cases could incur higher or lower costs depending on the intensity of treatment and length of stay.

### Table 7.8 Estimated average hospitalisation cost for a case of severe herpes zoster

| Age group | Estimated average hospitalisation cost for a case of severe herpes zoster[163, 173] |
|---|---|
| 0 to 9 years | €4,598 |
| 10 to 19 years | €5,207 |
| 20 to 29 years | €5,280 |
| 30 to 39 years | €5,826 |
| 40 to 49 years | €5,574 |
| 49 to 59 years | €5,064 |
| 60 to 69 years | €5,512 |
| 70 to 79 years | €5,344 |
| ≥80 years | €5,236 |

#### 7.3.1.8.5.2 Societal perspective

In addition to the costs included in the payer perspective (described above), the societal perspective also included the following costs for varicella, herpes zoster and post herpetic neuralgia:

- out of pocket expenses for those not eligible for a GP visit or medical card and who therefore incur personal cost to attend the GP and obtain prescription medication
- out of pocket expenses to obtain over the counter (OTC) medication
- productivity loss of paid work, due to absenteeism, for both those ill and those providing care to individuals sick with varicella, herpes zoster and post herpetic neuralgia.

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.[170] The cost of a GP visit for private patients was sourced from the literature,[171] inflated to 2022 Irish € (using the *Doctor's fees* sub index of the CSO's Consumer Price Index [CPI] monthly series data)[172] and estimated at €54.05. The mean cost of prescription medication per case of herpes zoster (€104.62) and post herpetic neuralgia (€101.88) for private patients was assumed to be the same as the opportunity cost of this medication to the HSE, described above for the payer perspective. It was also assumed that all private patients with herpes zoster and post herpetic neuralgia are prescribed medication.

The mean cost of OTC medication per case of varicella (including soothing gel and paracetamol) was estimated at €13.90 for age groups 1-3, €17.90 for age groups 4-8 and €11.20 for age groups 9-16. It was assumed that in general OTC medication is used in 50% of cases of varicella and breakthrough varicella and 100% of cases that develop severe varicella requiring hospitalisation.

Estimates of the productivity loss to society of paid work, due to absenteeism for varicella, herpes zoster and post herpetic neuralgia, were valued using the Human Capital Approach, by multiplying the days lost to health problems by median daily earnings.[174] For those ill, it was assumed that productivity losses only accrue to those greater than or equal to 15 years and less than 80 years of age who are working as part of the labour force. Labour force data published by the CSO were used to estimate the proportion of the population working for each age group of the model (Table 7.9).[175] Earnings analysis data published by the CSO[176] were used to estimate median daily earnings (in 2022) by age group (Table 7.9). It was assumed that five work days were lost for a case of either varicella, herpes zoster or post herpetic neuralgia that didn't require hospitalisation. In the case of hospitalised cases of varicella or herpes zoster, it was assumed that the number of work days lost was five plus the average length of stay (in days) in hospital. Data on average length of stay in hospital was based on HIPE discharge data provided by the HPO.[163]

In terms of estimating productivity losses associated with caring for ill individuals, it was assumed that those aged up to and including 14 years require care from a parent or guardian. Data from the European Union - Statistics on Income and Living Conditions (EU-SILC) Instrument[177] were used to estimate the proportion of households that may not have home cover in the event that a sick child requires care. The dataset provides household detail including the principal economic status of any adults and the age of any children. From these data we estimated the proportion of cases where home cover was unavailable in the event that a sick child (less than 15 years) required care. In the base case scenario, using an average of 2017-2021 data, it was estimated that 71.5% of households do not have home cover available in the event that a child is sick and would therefore be required to take leave from work. The daily earnings of a caregiver (€143.85) were estimated as the average of median earnings of those in age groups 20-29 years, 30-39 years, and 40-49 years. It was assumed that the average number of work days lost for caregivers for non-hospitalised cases was three days, and three days plus average length of stay (in days) in hospital for hospitalised cases. Data on average length of stay in hospital was based on HIPE discharge data provided by the HPO.[163]

### Table 7.9 Proportion of the population working and estimate of daily lost productivity to society by age group

| Age group | Proportion of the population working[175] | Estimate of median daily earnings[176] |
|---|---|---|
| 15 to 19 years | 28.52% | €69.13 |
| 20 to 29 years | 78.29% | €108.08 |
| 30 to 39 years | 83.32% | €155.38 |
| 40 to 49 years | 82.80% | €168.10 |
| 50 to 59 years | 79.82% | €159.95 |

| Age group | Proportion of the population working[175] | Estimate of median daily earnings[176] |
|---|---|---|
| 60 to 69 years | 42.09% | €119.79 |
| 70 to 79 years | 1.33% | €119.79 |

#### 7.3.1.8.6 Vaccination programme costs

For both the payer and societal perspectives, varicella vaccination programme costs were also included in the analysis. Programme costs included procurement, administration, national cold chain service, (storage and transportation of the vaccines), as well as education and communication about the varicella vaccination programme. Vaccine price information was not available, so a vaccine price of €32.73 (ex. VAT) was assumed for both the first dose and second dose, with no differentiation between the monovalent and quadrivalent MMRV vaccine. This was calculated as an average of the price of the GSK monovalent vaccine (£27.31) and the MSD monovalent vaccine (£30.30) used in a CEA of varicella vaccination for the UK, and using a currency exchange rate of €1/£0.88.[132] The cost for GP administration of one vaccine dose was assumed to be €19.73. This was estimated as an average of all contractual payments currently made to GPs for the current national childhood immunisation programmes.[178] In the case of the two-dose regimen, where the second dose is administered at five years of age under the schools programme, it was assumed that the additional cost of administering another vaccine, either a monovalent or quadrivalent MMRV vaccine, was also €19.73. The cost of vaccine administration may be lower than that in the GP practice because of efficiencies in a schools-based programme and the fact that the cost of administering may be distributed across four vaccines. However, as there was no reliable cost data from the schools programme to support calculating a more accurate figure, as such we have adopted a conservative approach. The costs of national cold chain service and education and communication about the varicella vaccination programme were assumed to be 3.9% and 1.5% of the vaccine procurement cost respectively. These figures were estimated based on historic national immunisation expenditure data.[179]

### 7.3.1.9 Model outputs

In the CUA, incremental costs and QALYs were estimated and then used to calculate the incremental cost-effectiveness ratio (ICER) – the incremental cost per QALY gained. In accordance with national HTA guidelines, the ICER was reported relative to willingness-to-pay (WTP) thresholds of €20,000 and or €45,000 per QALY, as appropriate.[139] 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.

#### 7.3.1.10 Assessment and quantification of uncertainty

Deterministic sensitivity analyses (DSA) and a truncated probabilistic sensitivity analysis (PSA) were conducted to test the robustness of the economic model outputs.

##### 7.3.1.10.1 Sensitivity analysis

Parameter uncertainty in the economic model were assessed using univariate sensitivity analysis. Specific parameter values were fixed in turn at lower and upper 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 tornado plots.

##### 7.3.1.10.2 Scenario analysis

In developing the economic model, a number of important assumptions were made regarding both structural and parameter uncertainty. Scenario analysis was conducted to assess these uncertainties, whereby model assumptions and base case parameter values were varied.

##### 7.3.1.10.3 Probabilistic sensitivity analysis

The robustness of the economic model results was also tested using PSA, which enables the joint uncertainty in model parameters to be assessed. In PSA, statistical distributions are assigned to input parameters, a random sample is drawn from the plausible range for each parameter, and the model is run using the random sample values. The model is rerun repeatedly to obtain a distribution for the measured outputs (that is, incremental costs and incremental QALYs). A truncated PSA was conducted where statistical distributions were assigned to a number of the epidemiological model input parameters (vaccination coverage, vaccine effectiveness and waning immunity) and all of the economic model input parameters. For each of the three vaccination strategies, a total of 30 simulations of the epidemiological model were run using a sample of parameter values generated using Latin hypercube sampling. The model output from each of the 30 simulations was then used in a further 250 simulations of the economic model for each vaccination strategy using randomly sampled parameter values. This produced a total of 7,500 simulations for each vaccination strategy. The results across the model replications were recorded and compared to the cost-utility results of the deterministic model.

#### 7.3.1.11 Model calibration and validation

Internal validation of the economic 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.

## 7.4 Results

### 7.4.1 Epidemiological analysis

The prevalence of varicella disease in Ireland generated by the epidemiological model, before vaccination was introduced to the model, approximated published estimated prevalence data (Appendix A7.4a). Similarly, the incidence of herpes zoster disease in Ireland generated by the epidemiological model, before the introduction of varicella vaccination, approximated incidence data that was estimated from Irish sentinel surveillance data of GP consultation rates for herpes zoster (Appendix A7.4b).

Following the introduction of varicella vaccination to the model, the predicted reduction in recovered varicella cases over 80 years, ranged from 24% for the one-dose strategy to 71% for the two-dose short interval strategy (Table 7.10). The predicted reduction in recovered herpes zoster cases with varicella vaccination ranged from 40% for the one-dose strategy to 50% for the two-dose short interval strategy over the 80 year time horizon of the model (Table 7.11).

**Table 7.10 Estimated change (%) (based on the epidemiological model output) in varicella recovered cases by year and vaccination strategy, versus no vaccination**

| Time | 1-dose | 2-dose short interval | 2-dose long interval |
|---|---|---|---|
| Baseline | 0.0% | 0.0% | 0.0% |
| Year 10 | -7.5% | -10.4% | -9.6% |
| Year 20 | -12.3% | -20.6% | -19.4% |
| Year 30 | -16.3% | -31.3% | -29.1% |
| Year 40 | -19.1% | -40.9% | -38.2% |
| Year 50 | -20.9% | -50.4% | -46.6% |
| Year 60 | -22.2% | -58.4% | -54.3% |
| Year 70 | -23.0% | -65.3% | -60.5% |
| Year 80 | -23.5% | -70.6% | -65.6% |

### Table 7.11 Estimated change (%) (based on the epidemiological model output) in herpes zoster recovered cases by year and vaccination strategy, versus no vaccination

| Time | 1-dose | 2-dose short interval | 2-dose long interval |
|---|---|---|---|
| Baseline | 0.0% | 0.0% | 0.0% |
| Year 10 | -0.4% | -0.4% | -0.4% |
| Year 20 | -1.6% | -2.0% | -1.9% |
| Year 30 | -4.0% | -5.1% | -4.8% |
| Year 40 | -7.9% | -10.1% | -9.7% |
| Year 50 | -13.8% | -17.6% | -16.9% |
| Year 60 | -21.6% | -27.5% | -26.5% |
| Year 70 | -30.5% | -38.9% | -37.5% |
| Year 80 | -39.5% | -50.3% | -48.7% |

## 7.4.2 Cost-utility analysis

### 7.4.2.1 Base case analysis

From the payer perspective, all three vaccination strategies under consideration were both more costly and more effective (fewer QALY losses) relative to no vaccination over an 80 year time horizon (Table 7.12).

### Table 7.12 Costs, benefits and average cost-effectiveness ratios (versus no vaccination) of varicella vaccination strategies

| Vaccination Strategy | Cost (€ million) | | Benefit (QALY Loss) | | ACER (versus no vaccination) |
|---|---|---|---|---|---|
| | Mean | Incremental | Mean | Incremental | |
| No vaccination | 152.8 | - | 25,423 | - | - |
| 1-dose | 190.0 | €37.2 | 21,150 | -4,274 | €8,712 |
| 2-dose short interval | 249.8 | €97.0 | 19,795 | -5,629 | €17,233 |
| 2-dose long interval | 241.1 | €88.3 | 20,018 | -5,406 | €16,331 |

**Key:** ACER – average cost-effectiveness ratio

To determine cost effectiveness, the incremental cost and incremental effect of each vaccination strategy was compared with the previous less expensive alternative strategy (Table 7.13 and Figure 7.2). No dominant vaccination strategies were identified in the incremental analysis. The incremental analysis also suggested that the two-dose long interval strategy may lie just off the cost-effectiveness efficiency frontier, with the ICER higher than that for the two-dose short interval strategy. However, given that the principle of extended dominance does not apply as alternative vaccination strategies cannot be combined in a single vaccination programme, the two-dose long interval strategy cannot be ruled out. For that reason, the two-dose short interval strategy was also compared with the one-dose strategy, producing an ICER of €44,106/QALY gained. Given the uncertainty associated with deterministic results alone, budget constraints that apply to increasingly costly strategies, and the similarity in ICERs between the two-dose

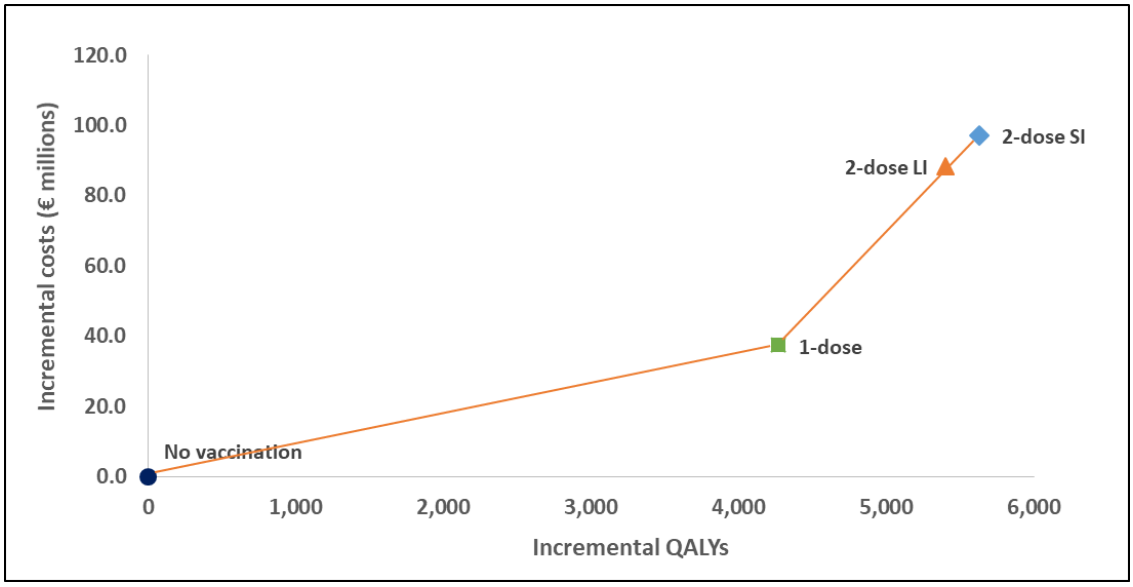
strategies relative to the one-dose strategy, both of which lie very closely to the WTP threshold of €45,000/QALY gained, the CUA has been conducted and reported based on the ICERs reported in Table 7.13.

### Table 7.13 Incremental costs and benefits of varicella vaccination strategies

| Strategy | Comparator | Cost (€ million) | | Benefits (QALYs) | | ICER |
|---|---|---|---|---|---|---|
| | | Total | Incremental | Total | Incremental | €/QALY |
| No vaccination | - | 152.8 | - | 0.0 | - | - |
| 1-dose | No vaccination | 190.0 | 37.2 | 4,274 | 4,274 | 8,712 |
| 2-dose LI | 1-dose | 241.1 | 51.1 | 5,406 | 1,132 | 45,090† |
| 2-dose SI | 2-dose LI | 249.8 | 8.7 | 5,629 | 223 | 39,112 |

**Key:** LI – long interval; QALY – quality adjusted life year; SI – short interval
†Principle of extended dominance does not apply.

### Figure 7.2 Efficiency frontier for varicella vaccination strategies on the incremental cost-effectiveness plane




**Key:** LI – long interval; QALY – quality adjusted life year; SI – short interval

From the payer perspective, over an 80 year time horizon, it was estimated that:

- a one-dose universal childhood varicella vaccination programme, with vaccination at 12 months of age, would be associated with an incremental cost of €37.2 million and a gain of 4,274 QALYs, producing an ICER of €8,712/QALY gained. A one-dose strategy would thus be considered cost-effective at a willingness to pay threshold of €20,000/QALY gained.
- a two-dose long interval programme, with vaccination at 12 months and five years of age, would be associated with an incremental cost of €51.1 million and a gain of 1,132 QALYs relative to a one-dose programme, producing an ICER of €45,090/QALY gained.

- a two-dose short interval programme, with vaccination at 12 months and 15 months of age, would be associated with an incremental cost of €8.7 million and a gain of 223 QALYs relative to a two-dose long interval programme, producing an ICER of €39,112/QALY gained.

From the societal perspective, all three vaccination strategies were estimated to dominate no vaccination, that is, they were less costly and generated QALY gains. This was mainly as a result of a reduction in productivity losses with vaccination due to a decline in the numbers developing varicella and herpes zoster and a resulting fall in absence from paid work for both those ill and their caregivers. When considered from the societal perspective, the estimated total cost savings with vaccination (relative to no vaccination) were €358 million, €389 million and €379 million for the one-dose, two-dose short interval, and two-dose long interval strategies, respectively. Overall, the two-dose short interval strategy generated the largest cost savings and largest QALY gains.

#### 7.4.2.2 Univariate sensitivity analysis

For the univariate sensitivity analysis, a number of input parameters from both the epidemiological and economic model were varied (Table 7.14) and ranked in order of increasing influence on uncertainty in the ICER. Results are presented as tornado plots which provide a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters. Only those parameters that result in at least a 5% fluctuation from the base case ICER are presented.

**Table 7.14 Parameters subject to univariate sensitivity analysis**

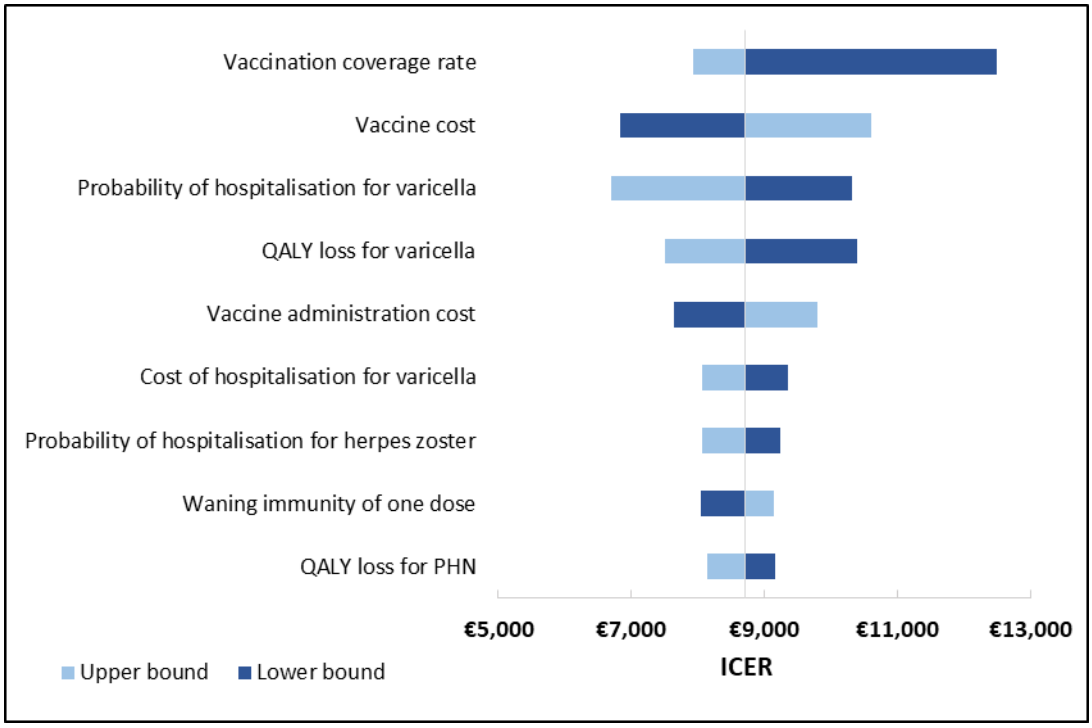
| Model | Parameter tested† | Base value | Lower bound | Upper bound |
|---|---|---|---|---|
| Epidemiological | Coverage rate | 0.88 | 0.70 | 0.93 |
| Epidemiological | Vaccine effectiveness: 1-dose strategy | 0.74 | 0.65 | 0.85 |
| Epidemiological | Vaccine effectiveness: 2-dose strategy¥ | 0.91 | 0.85 | 0.95 |
| Epidemiological | Force of infection in vaccinated individuals | 0.73 | 0.50 | 1.00 |
| Epidemiological | Waning immunity (per annum): one dose | 0.04 | 0.02 | 0.06 |
| Economic | Vaccine cost | €32.73 | €26.18 | €39.28 |
| Economic | Vaccine administration cost | €19.73 | €15.78 | €23.68 |
| Economic | QALY loss with varicella§ | Various | Various | Various |
| Economic | QALY loss with herpes zoster§ | Various | Various | Various |
| Economic | QALY loss with post herpetic neuralgia§ | Various | Various | Various |
| Economic | QALY loss with mild adverse events after vaccination§ | Various | Various | Various |
| Economic | Probability of hospitalisation with varicella§ | Various | Various | Various |
| Economic | Probability of hospitalisation with herpes zoster§ | Various | Various | Various |
| Economic | Probability of post herpetic neuralgia§ | Various | Various | Various |
| Economic | Cost of hospitalisation for varicella§ | Various | Various | Various |
| Economic | Cost of hospitalisation for herpes zoster§ | Various | Various | Various |

**Key:** QALY - quality adjusted life year;
†Base case values, lower and upper bounds, and sources for all epidemiological parameters are provided in Tables 7.1 and 7.2 and for all economic parameters in Appendix A7.3.
¥ The lower bound value represents a combination of lower bound effectiveness for both first and second dose. The bound applied to the one-dose strategy was the same as the first dose effectiveness in the two-dose strategy.
§ These parameters included age-specific values for each of the 16 age groups. In setting one of these parameters to their upper or lower bound, the values across all 16 age bands were simultaneously set at their upper and lower band values.

#### 7.4.2.2.1 One-dose vaccination strategy versus no vaccination

The univariate sensitivity analysis demonstrated that the results for the one-dose strategy, relative to no vaccination, were robust to variation in input parameters (Figure 7.3). From the payer perspective, the ICER for the one-dose strategy did not exceed the WTP threshold of €20,000/QALY gained in any of the investigated sensitivity analyses. The ICER was most sensitive to a change in the coverage rate to 70%, the cost of the vaccine, the probability of hospitalisation for varicella and the QALY loss associated with varicella. A one percentage point reduction or increase in the discount rate did not impact on the interpretation of the cost-effectiveness of the one-dose strategy with the ICER ranging from €7,573 to €9,697/QALY gained.

**Figure 7.3 Tornado plot of univariate sensitivity analysis for a one-dose vaccination strategy versus no vaccination over an 80 year time period†**



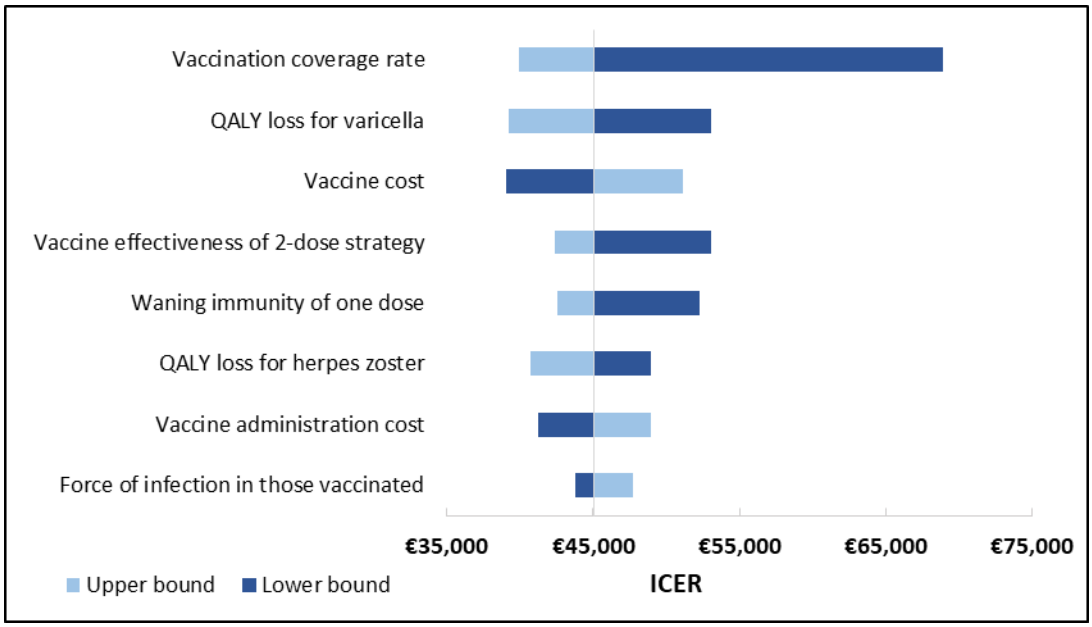

**Key:** PHN – post herpetic neuralgia; QALY – quality adjusted life year.
†Parameters are ranked in order of decreasing influence on the ICER. Only the most influential parameters are shown.

#### 7.4.2.2.2 Two-dose long interval versus one-dose vaccination strategy

The univariate sensitivity analysis demonstrated that the ICER for the two-dose long interval strategy, relative to the one-dose strategy, was most sensitive to changes in the coverage rate, the QALY loss associated with varicella, the cost of the vaccine, the vaccine effectiveness of a two-dose strategy, and waning immunity of one dose. (Figure 7.4). In summary, from the payer perspective, the ICERs for the two-dose long interval strategy were:

- €68,901/QALY gained when the coverage rate was set at the lower bound of 70% and €39,954/ QALY gained when set at the upper bound of 93%
- €53,408/QALY gained and €39,208/QALY gained when the QALY loss for varicella was set at the lower bounds and upper bounds respectively
- €39,059/QALY gained when the cost of the vaccine was set at the lower bound of €26.18 and €51,121/QALY gained when set at the upper bound of €39.28
- €53,036/QALY gained when the vaccine effectiveness of a two-dose strategy was set to the lower bound of 85% and €42,410/QALY when set to the upper bound of 95%
- €52,305/QALY gained when the waning immunity for one vaccine dose was set to the lower bound of 2% per annum and €42,253 when set to the upper bound of 6% per annum.
- A one percentage point reduction or increase in the discount rates had minimal impact on the cost-effectiveness of the two-dose long interval strategy.

**Figure 7.4 Tornado plot of univariate sensitivity analysis for a two-dose long interval vaccination strategy, versus a one-dose strategy, over an 80 year time period†**



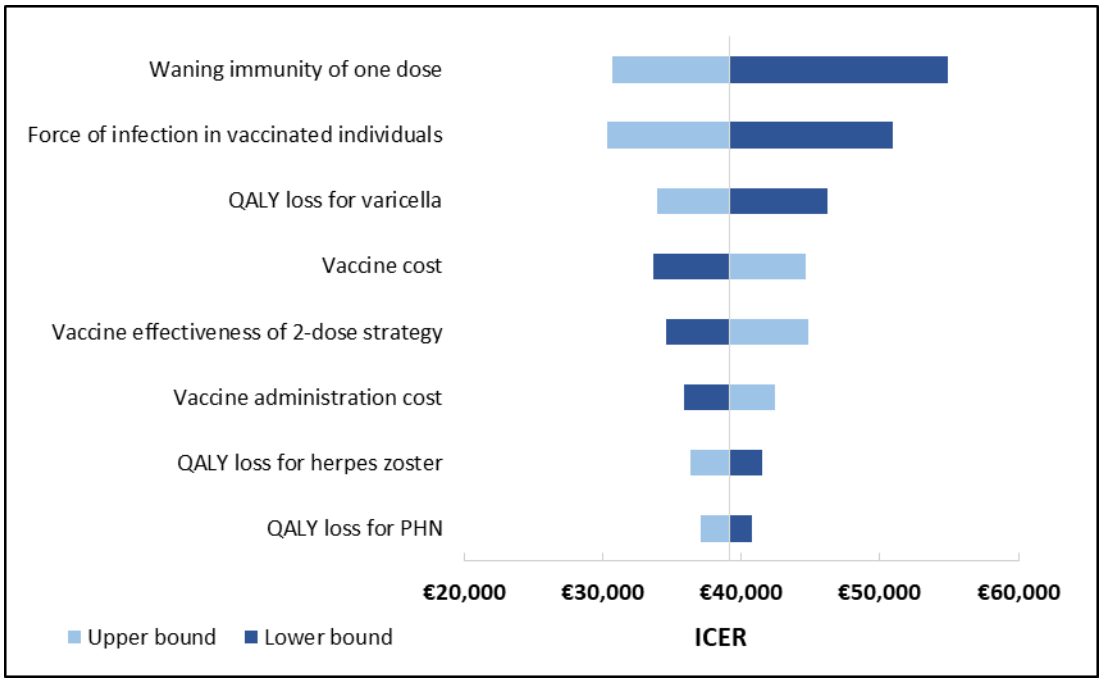

**Key:** QALY – quality adjusted life year.
†Parameters are ranked in order of decreasing influence on the ICER. Only the most influential parameters are shown.

#### 7.4.2.2.3 Two-dose short interval versus two-dose long interval vaccination strategy

The univariate sensitivity analysis demonstrated that the ICER for the two-dose short interval strategy, relative to the two-dose long interval strategy, was most sensitive to changes in waning immunity of one dose, the force of infection in vaccinated individuals and the QALY loss associated with varicella (Figure 7.5). In summary, from the payer perspective, the ICERs for the two-dose short interval strategy were:

- €54,922/QALY gained when waning immunity for one vaccine dose was set to the lower bound of 2% per annum and €30,623/QALY gained when set to the upper bound of 6% per annum.
- €30,250/QALY gained when the force of infection in vaccinated individuals vaccine was set at the lower bound (half that of vaccinated individuals) and €50,970/QALY gained when set at the upper bound (equivalent to non-vaccinated individuals)
- €46,251/QALY gained and €33,882/QALY gained when the QALY loss for varicella was set at the lower bounds and upper bounds respectively
- A one percentage point reduction in the discount rates improved the cost-effectiveness of the two-dose short interval strategy (from €39,112 to €30,487/QALY gained), relative to the two-dose long interval strategy. However, a one percentage point increase in the discount rate resulted in an increase in the ICER from €39,112 to €48,131/QALY gained.

**Figure 7.5 Tornado plot of univariate sensitivity analysis for a two-dose short interval vaccination strategy, versus a two-dose long interval strategy, over an 80 year time period†**




**Key:** QALY – quality adjusted life year.
†Parameters are ranked in order of decreasing influence on the ICER. Only the most influential parameters are shown

### 7.4.2.3 Scenario analysis

The following scenario analyses were modelled to test a number of assumptions made when developing the models:

- Inclusion of full temporary exogenous boosting
- Worst case vaccine uptake for the two-dose strategies
- Alternative vaccine cost
- Alternative costs for vaccine administration by GPs
- Alternative costs for vaccine administration by the HSE under the schools immunisation programme

*Inclusion of full temporary exogenous boosting*

The exogenous boosting theory posits that those who are susceptible to reactivation of dormant VZV receive an immunity boost when exposed to VZV, thereby delaying potential VZV reactivation and the development of herpes zoster. If the theory holds, the introduction of a varicella vaccination programme could potentially result in an increase in incidence of herpes zoster due to a reduction in circulating VZV. The

inclusion of exogenous boosting in the model allows individuals to move temporarily from the 'susceptible to herpes zoster' state, back to the 'recovered from varicella' state.[141]

The assumption of full temporary exogenous boosting resulted in a reduction in the overall number of recovered herpes zoster cases over the lifetime of the model. However, a temporary increase (from baseline to year 20) in the number of recovered herpes zoster cases in the five age groups from 15 to 19 years to 50 to 59 years inclusive for all three vaccination strategies was observed, when compared with no vaccination (Table 7.15). In terms of cost-effectiveness, the one-dose strategy remained cost-effective, relative to no vaccination, at a WTP threshold of €20,000/QALY gained. The ICER for the two-dose long interval strategy, relative to the one-dose strategy, was above the WTP threshold of €45,000/QALY gained at €68,966/QALY gained. Similarly, the ICER for the two-dose short interval strategy, relative to the one-dose strategy was also above the WTP threshold of €45,000/QALY gained, at €65,214/QALY gained.

**Table 7.15 Estimated change (%) (based on the epidemiological model output) in herpes zoster recovered cases by year and vaccination strategy, versus no vaccination, when exogenous boosting assumed**

| Time | 1-dose | 2-dose short interval | 2-dose long interval |
|---|---|---|---|
| Baseline | 0.0% | 0.0% | 0.0% |
| Year 10 | 0.6% | 1.1% | 1.0% |
| Year 20 | -0.3% | 1.0% | 0.8% |
| Year 30 | -2.9% | -1.3% | -1.3% |
| Year 40 | -7.3% | -6.1% | -6.0% |
| Year 50 | -13.7% | -13.8% | -13.3% |
| Year 60 | -21.9% | -24.1% | -23.3% |
| Year 70 | -31.0% | -36.0% | -34.8% |
| Year 80 | -40.1% | -48.0% | -46.4% |

*Worst case vaccine uptake for the two-dose strategies*

A scenario was modelled to account for a perception that varicella may be a mild disease, potentially resulting in lower vaccine uptake than current childhood vaccination programmes. Uptake of dose one was set at the lower bound (70%) used in the univariate sensitivity analysis and uptake of dose two was similarly set at 70%, resulting in overall population coverage of 49% for the two-dose strategies.

In a scenario that tested the vaccination uptake rate, it was assumed that uptake for dose one and dose two were both 70%, resulting in 49% population coverage for the two-dose strategies. The ICER for the two-dose long interval strategy, relative to the one-dose strategy, was €107,326/QALY gained and for the two-dose short interval strategy, relative to the long interval strategy, was €59,918/QALY gained.

*Alternative vaccine cost*

There is considerable uncertainty with regard to the cost of the vaccine and therefore, in addition to the univariate sensitivity conducted above, the cost was set at a number of values up to 50% higher than the base-case value. When the vaccine cost was set at €40.00 per dose, the one-dose strategy remained cost-effective at a WTP threshold of €45,000/QALY gained (ICER of €10,806/QALY gained). The ICER for the two-dose long interval strategy, relative to the one-dose strategy, increased to €51,788/QALY gained and that for the two-dose short interval strategy, relative to the long interval strategy, was €45,200/QALY gained. At a cost of €50.00 per vaccine dose, the one-dose strategy remained cost-effective at a WTP threshold of €45,000/QALY gained (ICER of €13,687/QALY gained). The ICER for the two-dose long interval strategy, relative to the one-dose strategy, increased to €61,001/QALY gained and that for the two-dose short interval strategy, relative to the long interval strategy, was €53,574/QALY gained.

*Alternative costs for vaccine administration by GPs.*

The potential addition of a new vaccine to the childhood immunisation schedule may have resource implications for GP practices that have not been accounted for in the base case analysis. Therefore, in the scenario analysis, the GP vaccine administration cost for the first dose in all three strategies and the second dose in the two-dose short interval strategy was set at values above the upper bound (€23.68) used in the univariate sensitivity analysis.

When the GP vaccine administration cost was set at €25.00, €30.00 and €35.00, the one-dose strategy, relative to no vaccination, remained cost-effective at WTP thresholds below €20,000/QALY gained. The ICERs for the two-dose long interval strategy, relative to the one-dose strategy, ranged from €45,383/QALY gained (when the GP administration cost was set at €25.00), to €45,940/QALY gained (when the GP administration cost was set at €35.00). The ICERs for the two-dose short interval strategy, relative to the long interval strategy were above the WTP threshold of €45,000/QALY gained and ranged from €68,188/QALY gained (when the GP administration cost was set at €25.00), to €123,631/QALY gained (when GP administration cost was set at €35.00).

*Alternative costs for vaccine administration by the HSE under the schools immunisation programme*

Currently, the schools immunisation programme aims to vaccinate students in junior infants of primary school and age equivalent students in special schools and those home schooled with the 4 in 1 and MMR vaccines. While there is uncertainty around the additional cost of administering the second varicella vaccine dose as part of the

schools programme, there is also the possibility that the single quadrivalent MMRV vaccine may be used instead of both the MMR and monovalent varicella vaccines. A number of scenarios were therefore modelled where the vaccine administration cost for the second dose in the two-dose long interval strategy was set at values below the lower bound (€15.78) used in the univariate sensitivity analysis. In scenarios where the HSE vaccine administration cost for the second dose was set at both €15.00 and €10.00, the two-dose long interval strategy was cost-effective, relative to the one-dose strategy, at a WTP threshold of €45,000/QALY gained, with ICERs of €40,732 and €36,125 per QALY gained respectively. The results for all scenarios are presented in Table 7.16.

### Table 7.16 Results of scenario analyses over an 80 year time horizon (payer perspective)

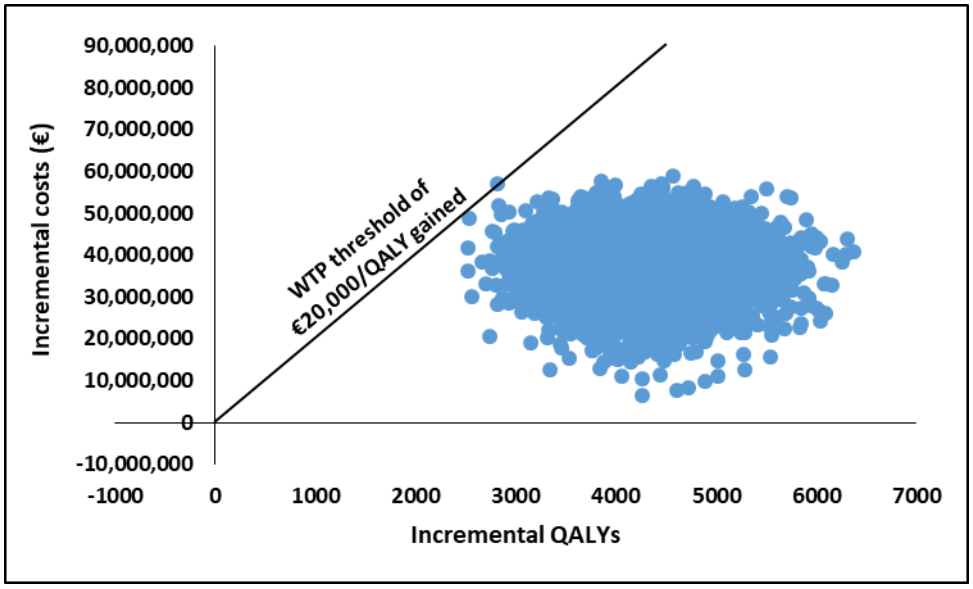
| Scenario | Vaccination strategy | Comparator | Incremental Costs (€ million) | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|
| Full temporary exogenous boosting | 1-dose | No vaccination | €37.9 | 4,188 | €9,051 |
| | 2-dose LI | 1-dose | €53.4 | 775 | €68,966 |
| | 2-dose SI | 2-dose LI | €9.0 | 183 | €49,282 |
| 70% uptake for both vaccine doses, resulting in 49% population coverage for 2-dose strategies | 2-dose LI | 1-dose | €54.0 | 503 | €107,326 |
| | 2-dose SI | 2-dose LI | €9.1 | 153 | €59,918 |
| Vaccine cost @ €40.00 | 1-dose | No vaccination | €46.2 | 4,274 | €10,806 |
| | 2-dose LI | 1-dose | €58.6 | 1,132 | €51,788 |
| | 2-dose SI | 2-dose LI | €10.1 | 223 | €45,200 |
| Vaccine cost @ €45.00 | 1-dose | No vaccination | €52.3 | 4,274 | €12,247 |
| | 2-dose LI | 1-dose | €63.8 | 1,132 | €56,394 |
| | 2-dose SI | 2-dose LI | €11.0 | 223 | €49,387 |
| Vaccine cost @ €50.00 | 1-dose | No vaccination | €58.5 | 4,274 | €13,687 |
| | 2-dose LI | 1-dose | €69.1 | 1,132 | €61,001 |
| | 2-dose SI | 2-dose LI | €11.9 | 223 | €53,574 |
| GP vaccine administration cost for the first dose set @ €25.00 | 1-dose | No vaccination | €43.4 | 4,274 | €10,153 |
| | 2-dose LI | 1-dose | €51.4 | 1,132 | €45,383 |
| | 2-dose SI | 2-dose LI | €15.2 | 223 | €68,188 |
| GP vaccine administration cost for the first dose set @ €30.00 | 1-dose | No vaccination | €49.2 | 4,274 | €11,519 |
| | 2-dose LI | 1-dose | €51.7 | 1,132 | €45,662 |
| | 2-dose SI | 2-dose LI | €21.3 | 223 | €95,775 |
| GP vaccine administration cost for the first dose set @ €35.00 | 1-dose | No vaccination | €55.1 | 4,274 | €12,886 |
| | 2-dose LI | 1-dose | €52.0 | 1,132 | €45,940 |
| | 2-dose SI | 2-dose LI | €27.5 | 223 | €123,361 |
| HSE vaccine administration cost for the second dose set @ €15.00 | 2-dose LI | 1-dose | €46.1 | 1,132 | €40,732 |
| | 2-dose SI | 2-dose LI | €13.7 | 223 | €61,248 |
| HSE vaccine administration cost for the second dose set @ €10.00 | 2-dose LI | 1-dose | €40.9 | 1,132 | €36,125 |
| | 2-dose SI | 2-dose LI | €18.9 | 223 | €84,647 |

**Key:** GP - general practitioner; HSE - Health Service Executive; LI - long interval; SI – short interval; QALY – quality adjusted life year

#### 7.4.2.4 Probabilistic sensitivity analysis

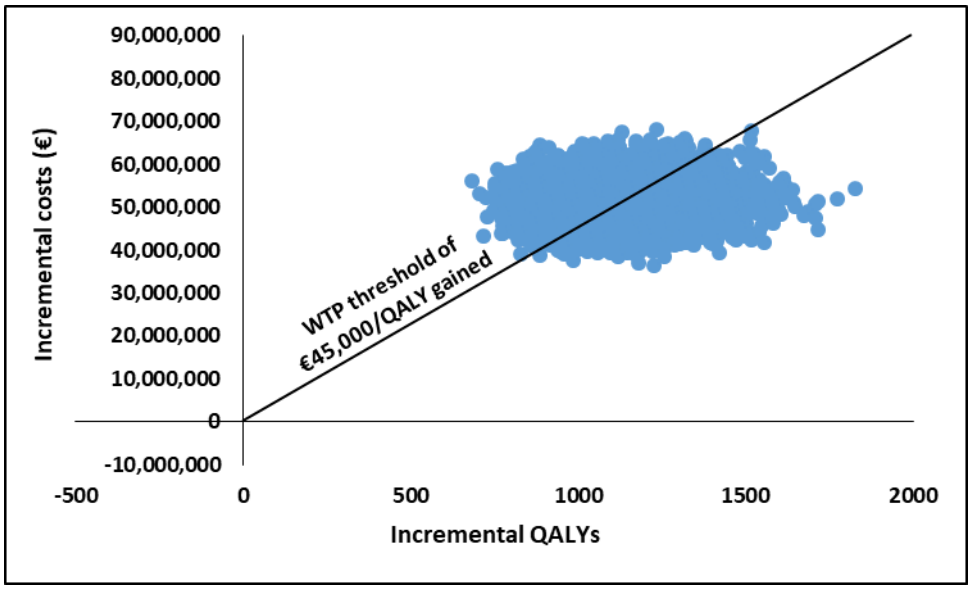
The results of the exploratory PSA demonstrate the robustness of the deterministic cost-effectiveness results of the one-dose vaccination strategy. The cost-effectiveness plane comparing one-dose varicella vaccination with no vaccination is presented in Figure 7.6 below. All point estimates lie in the north-east quadrant of the cost-effectiveness plane (where the intervention is more costly, but also more effective) and indicate cost-effectiveness at a WTP threshold of €20,000/QALY gained. The PSA results relating to the two-dose strategies highlight the uncertainty with regard to whether the two-dose long interval strategy lies on the cost-effectiveness frontier (Figure 7.7), the relative positions of the two-dose strategies on the frontier (Figure 7.8) and therefore their associated cost-effectiveness at a WTP threshold of €45,000/QALY gained. The probability that the two-dose long interval strategy lies on the cost-effectiveness frontier is 41% and the probability that the ICER for the two-long dose interval strategy, relative to the one-dose strategy, is less than or equal to €45,000/QALY gained is 47%.

**Figure 7.6 Cost-effectiveness plane of one-dose varicella vaccination strategy versus no-vaccination**



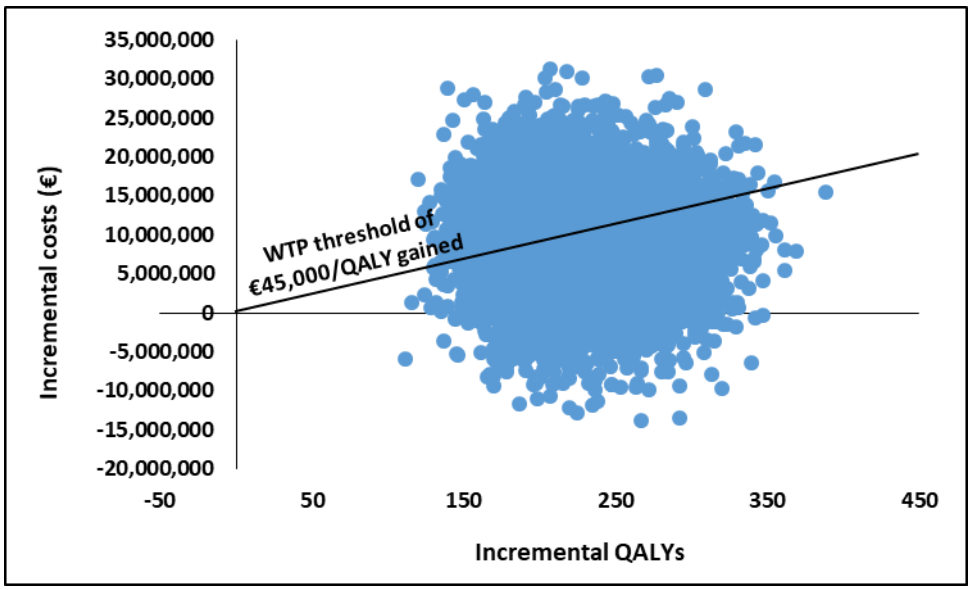

**Key:** QALYs – quality adjusted life years; WTP - willingness to pay

## Figure 7.7 Cost-effectiveness plane of two-dose long interval versus one-dose varicella vaccination strategy




**Key:** QALYs – quality adjusted life years; WTP - willingness to pay

## Figure 7.8 Cost-effectiveness plane of two-dose short interval versus two-dose long interval varicella vaccination strategy




### 7.4.3 Budget impact analysis

The BIA for each of the three vaccination strategies is presented relative to no vaccination. Based on the number of births in Ireland in 2021, it assumes an annual eligible population of 60,000 and vaccination uptake of 88% per the base case scenario.[2] The budget impact is limited to the vaccination programme costs, (including vaccine procurement, 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. Potential organisational issues associated with the introduction of a universal childhood varicella vaccination programme are described in chapter 8.

#### 7.4.3.1 Base case analysis

The five-year budget impact (Table 7.17) of a universal childhood varicella vaccination programme was estimated at:

- €13.1 million for the one-dose strategy
- €28.1 million for the two-dose short interval strategy, and
- €16.1 million for the two-dose long interval strategy.

The lower budget impact for the two-dose long interval strategy reflects the fact that only one birth cohort would complete the two-dose schedule within the five year time horizon of the BIA. The majority of vaccination programme expenditure (96.5%) for each strategy over the five year time horizon directly relates to vaccine procurement (64.8%) and vaccine administration (31.7%). For each of the three vaccination strategies, the costs averted over the five years, due to the reduction in incidence of both varicella and herpes zoster, was estimated at in excess of €3 million, largely due to a reduction in the number of hospitalisations for varicella. An itemised breakdown of the costs incurred and averted is provided in Appendix A7.5.

**Table 7.17 Five-year estimated budget impact (€ million) per vaccination strategy**

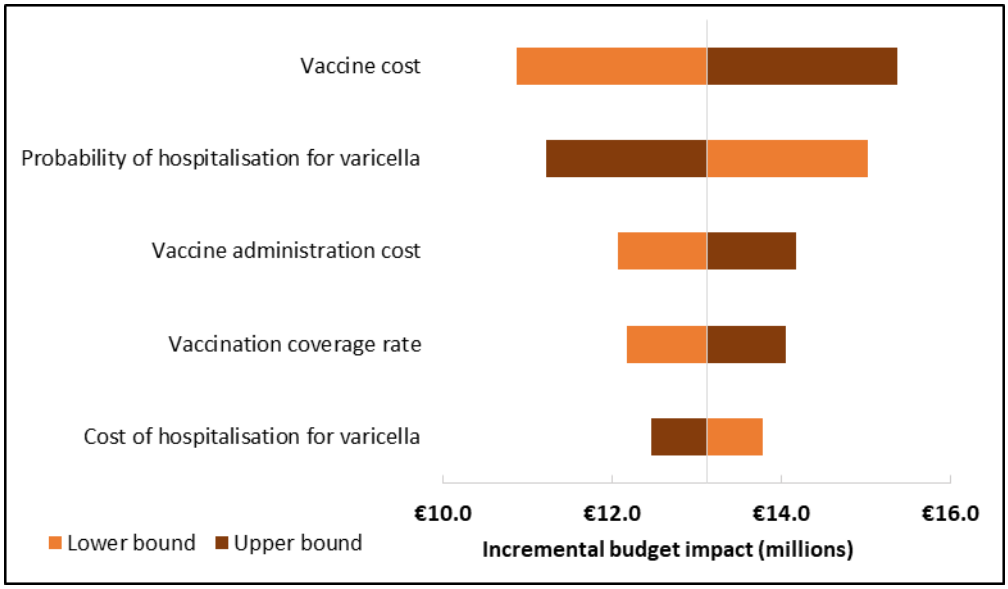
| **Strategy** | **1-dose** | | |
|---|---|---|---|
| **Year** | **Costs incurred** | **Costs averted** | **Budget impact** |
| Year 1 | €3.3 | €0.7 | €2.6 |
| Year 2 | €3.3 | €0.7 | €2.6 |
| Year 3 | €3.3 | €0.6 | €2.7 |
| Year 4 | €3.3 | €0.7 | €2.6 |
| Year 5 | €3.3 | €0.6 | €2.6 |
| **Total** | **€16.4** | **€3.3** | **€13.1** |
| **Strategy** | **2-dose short interval** | | |
| **Year** | **Costs incurred** | **Costs averted** | **Budget impact** |
| Year 1 | €5.7 | €0.8 | €5.8 |
| Year 2 | €6.6 | €0.7 | €5.8 |
| Year 3 | €6.6 | €0.7 | €5.9 |
| Year 4 | €6.6 | €0.8 | €5.7 |
| Year 5 | €6.6 | €0.8 | €5.7 |
| **Total** | **€32.0** | **€3.9** | **€28.1** |
| **Strategy** | **2-dose long interval** | | |
| **Year** | **Costs incurred** | **Costs averted** | **Budget impact** |
| Year 1 | €3.3 | €0.7 | €2.6 |
| Year 2 | €3.3 | €0.7 | €2.6 |
| Year 3 | €3.3 | €0.7 | €2.6 |
| Year 4 | €3.3 | €0.8 | €2.5 |
| Year 5 | €6.6 | €0.8 | €5.8 |

| Strategy | 1-dose | | |
|---|---|---|---|
| Year | Costs incurred | Costs averted | Budget impact |
| Total | €19.7 | €3.6 | €16.1 |

### 7.4.3.2 Univariate sensitivity analysis

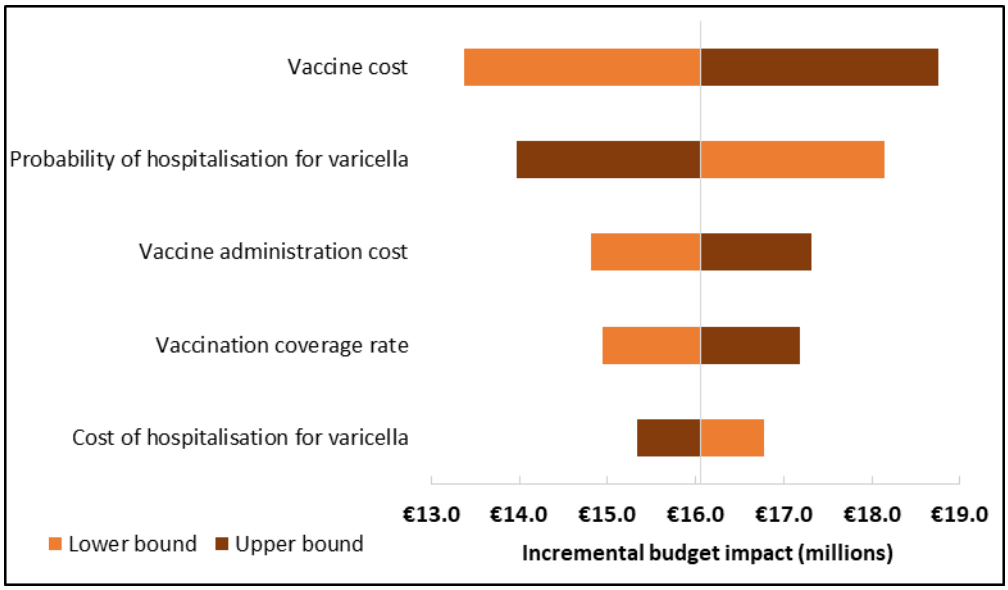
As in the CUA, univariate sensitivity analysis was undertaken to assess the impact of variations in input parameters on the five-year budget impact of introducing a universal childhood varicella vaccination programme. Of the five input parameters tested in the univariate sensitivity analysis, uncertainty relating to the cost of the vaccine was found to contribute most to the budget impact of all three vaccination strategies, followed by the probability of hospitalisation for varicella. Tornado plots are presented below for all three vaccination strategies (Figures 7.96, 7.10 and 7.11).

**Figure 7.9 Tornado plot of univariate sensitivity analysis for the five-year budget impact analysis for a one-dose vaccination strategy†**



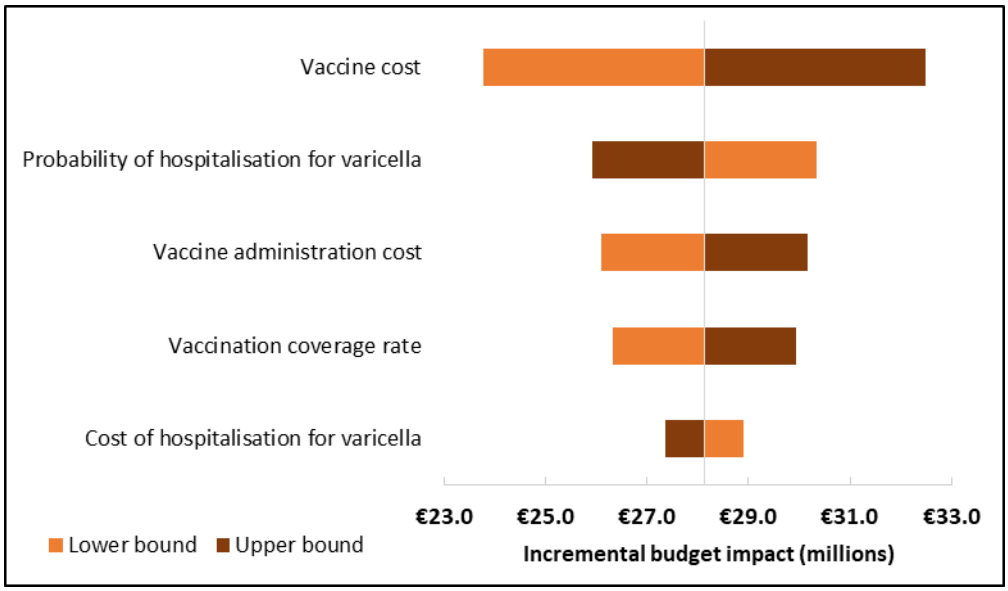

†For the budget impact analysis, VAT was applied to the cost of the vaccine.

**Figure 7.10 Tornado plot of univariate sensitivity analysis for the five-year budget impact analysis for a two-dose long interval vaccination strategy†**




†For the budget impact analysis, VAT was applied to the cost of the vaccine.

**Figure 7.11 Tornado plot of univariate sensitivity analysis for the five-year budget impact analysis for a two-dose short interval vaccination strategy†**




†For the budget impact analysis, VAT was applied to the cost of the vaccine.

### 7.4.3.3 Scenario analysis

In the BIA it was estimated that the cost of vaccine procurement and vaccine administration comprises 96.5% of the total vaccination programme costs for all three vaccination strategies. However, as highlighted in the CUA, there is uncertainty

with regard to both costs. Therefore, in addition to the univariate sensitivity analysis above, the following scenario analyses were conducted for the BIA:

- the cost of the vaccine was set at values above the upper bound (€39.28 + VAT) used in the univariate sensitivity analysis
- the cost payable to GPs for administering the single dose in the one-dose strategy, the first dose in the two-dose long interval strategy, and both doses in the two-dose short interval strategy, was set at values above the upper bound (€23.68) used in the univariate sensitivity analysis
- the cost payable to the HSE for administering the second dose in the two-dose long interval strategy was set at values below the lower bound (€15.78) used in the univariate sensitivity analysis.

Results presented in Table 7.18 highlight the budget impact when vaccine procurement costs and vaccine administration costs payable to GPs are set at values outside the ranges used in the univariate sensitivity analyses. With regard to the cost of the vaccine, divergence of the budget impact from the base case ranged from 17.3% for the two-dose short interval strategy when the vaccine cost was set at €40.00 plus VAT, to 45.1% for the one-dose strategy when the cost was set at €50.00 plus VAT. Divergence of the budget impact from the base case ranged from 8.7% for the two-dose long interval strategy when the vaccine administration cost was set at €25.00, to 30.7% for the one-dose strategy when the administration cost was set at €35.00. It should be noted that the difference in timing of the second dose for the two-dose strategies impacts on the relative impact of a change in administration cost that can be observed in a five year BIA.

### Table 7.18 Results of scenario analysis for the five-year budget impact analysis

| Scenario | Vaccination strategy | Total incremental cost (€ million) | Divergence from base case† |
|---|---|---|---|
| Vaccine cost (per dose) @ €40.00 + VAT (€49.20) | 1-dose | 15.6 | 19.0% |
| | 2-dose LI | 19.0 | 18.6% |
| | 2-dose SI | 33.0 | 17.3% |
| Vaccine cost (per dose) @ €45.00 + VAT (€55.35) | 1-dose | 17.3 | 32.0% |
| | 2-dose LI | 21.1 | 31.4% |
| | 2-dose SI | 36.3 | 29.1% |
| Vaccine cost (per dose) @ €50.00 + VAT (€61.50) | 1-dose | 19.0 | 45.1% |
| | 2-dose LI | 23.2 | 44.2% |
| | 2-dose SI | 39.7 | 41.0% |
| GP vaccine administration cost for the first dose for all strategies and second dose for 2-dose SI strategy set @ €25.00 | 1-dose | 14.5 | 10.6% |
| | 2-dose LI | 17.5 | 8.7% |
| | 2-dose SI | 30.8 | 9.6% |
| GP vaccine administration cost for the first dose for all strategies and | 1-dose | 15.8 | 20.7% |
| | 2-dose LI | 18.8 | 16.9% |

| Scenario | Vaccination strategy | Total incremental cost (€ million) | Divergence from base case† |
|---|---|---|---|
| second dose for 2-dose SI strategy set @ €30.00 | 2-dose SI | 33.4 | 18.8% |
| GP vaccine administration cost for the first dose for all strategies and second dose for 2-dose SI strategy set @ €35.00 | 1-dose | 17.1 | 30.7% |
| | 2-dose LI | 20.1 | 25.1% |
| | 2-dose SI | 36.0 | 27.9% |
| HSE vaccine administration cost for the second dose set @ €15.00 | 2-dose LI | 15.8 | -1.6% |
| HSE vaccine administration cost for the second dose set @ €10.00 | 2-dose LI | 15.5 | -3.2% |

**Key:** GP - general practitioner; HSE - Health Service Executive; LI - long interval; SI – short interval
†Percentage change in the total incremental budget impact over five years under the scenario analysis relative to the base case estimate.

## 7.5 Discussion

A de novo dynamic transmission model was developed to firstly characterise the incidence of both varicella and herpes zoster diseases in Ireland in the absence of varicella vaccination, and secondly to assess the impact of the introduction of routine childhood varicella vaccination on disease incidence. Three different varicella vaccination strategies, one-dose, two-dose short interval and two-dose long interval, were analysed. The epidemiological model output was subsequently used in an economic model to estimate the cost-effectiveness and budget impact of the introduction of routine childhood varicella vaccination in Ireland. The analysis of cost-effectiveness was conducted from both the payer (HSE) and societal perspectives, while the budget impact estimated the incremental cost to the HSE of implementing a varicella vaccination programme over a five year time horizon.

### 7.5.1 Main findings

Results from the epidemiological model indicate that overall incidence of both varicella and herpes zoster diseases is expected to fall after the introduction of varicella vaccination. Over the 80 year time horizon of the model, the vaccination strategy with the largest predicted percentage fall in recovered varicella cases (71%), relative to no vaccination, was the two-dose short interval strategy. This was followed by the two-dose long interval strategy and one-dose strategy with predicted falls of 66% and 24% respectively in the number of recovered varicella cases over the lifetime of the model. Almost 60% of varicella cases in the one-dose model were breakthrough cases. The difference in the reduction in recovered varicella cases between the two-dose strategies reflects waning immunity associated with a single dose and the different dosage intervals between the two strategies.

In terms of cost-effectiveness, the one-dose strategy was estimated to be cost-effective from the payer perspective, with an ICER of €8,712/QALY gained. The ICER for the next least expensive strategy, two-dose long interval, was estimated at €45,090/QALY gained. Both two-dose strategies were more costly and also more

effective than the one-dose strategy. In the base case analysis, the two-dose long interval strategy was just above the cost-effectiveness frontier. The results of the univariate and truncated probabilistic sensitivity analysis highlight the uncertainty in the ICERs for the two-dose strategies. However, the base case estimate of the cost of administering the second dose for the long interval strategy is considered very conservative, and, based on the scenario analysis results for that parameter value, it is likely that it may be on the cost-effectiveness frontier. From the payer perspective neither two-dose strategies would be considered cost-effective at a WTP threshold of €20,000/QALY gained. From the societal perspective all three vaccination strategies dominated no vaccination, where they were significantly less costly and more effective. Comparing the three vaccination strategies, the two-dose short interval dominated, being loss costly and more effective than both the one-dose and the two-dose long interval.

The univariate sensitivity analysis indicated that the cost-effectiveness results were most sensitive to changes in the vaccination programme uptake rate. However, when the uptake rate was set to the lower bound of 70%, the one-dose strategy remained cost-effective with respect to a WTP threshold of €20,000/QALY gained (ICER of €12,483/QALY gained). Overall, the univariate sensitivity analysis demonstrated that the cost-effectiveness results for the one-dose strategy were robust to variation in the model input parameters. With regard to the two-dose strategies, the deterministic ICERs, relative to the one-dose strategy, both lie close to €45,000/QALY gained. As highlighted in the univariate sensitivity analyses, there is a lot of uncertainty with regard to the two-dose ICERs and it is difficult to ascertain, with confidence, if the two-dose strategies are cost-effective relative to the one-dose strategy at a WTP threshold of €45,000/QALY gained. Overall, the results suggest that there is very little difference in cost-effectiveness between the two-dose strategies and any preference of one strategy over the other may rest with the organisational issues associated with implementation. A final decision with regard to the choice between a one- and two-dose strategy possibly lies within the stated objective of such a programme and whether that is to eliminate the disease or reduce hospitalisations and complications associated with varicella.

In terms of budget impact, the one-dose strategy was the least costly (€13.1 million) over a five year time period, followed by the two-dose long interval strategy (€16.1 million). The lower budget impact for the two-dose long interval strategy reflects the fact that only one birth cohort will complete the two-dose schedule within the five year time horizon of the BIA. From year five onwards, the difference in cost between the two-dose strategies should only reflect the difference in cost (if any) between administering the vaccine in the GP practice setting and the school setting. The cost of vaccine procurement and administration comprised the majority (96.5%) of the budget impact associated with the introduction of a varicella vaccination programme.

The predicted reduction in varicella cases and associated fall in the number of hospitalised cases contributed to cost savings in the short term. While the univariate sensitivity analysis indicated that the budget impact was most sensitive to changes in the cost of the vaccine, the scenario analysis also highlighted the potential budget impact if the vaccine administration cost payable to GPs exceeded the upper bound of €23.68 used in the sensitivity analysis. An increase to €25.00 in the cost payable to GPs would result in an increase in the base case budget impact of between 8.7% and 10.6%, depending on the vaccination strategy.

### 7.5.2 Limitations

The present study is subject to a number of limitations. As with any modelling exercise, both epidemiological and economic, the applicability of the findings is dependent on the underlying assumptions that underpin the model structure and the chosen parameter values. For the epidemiological model presented, a steady state population was assumed where the number of births was constant each year for the 80 year time horizon of the model. In reality, there are annual fluctuations in the birth rate and ongoing migration flows, both of which impact on the true population size and the age distribution of the population. In the case of an age-structured dynamic transmission model, where the force of infection differs between different age groups and is a function of the interaction between age groups, changes in the population distribution may impact the incidence of disease. Additionally, inward migration may be associated with populations that have not been vaccinated against varicella, and therefore may impact on the incidence of disease and associated breakthrough infection. However, the age distribution of the population in the younger age groups, where incidence of varicella is highest and vaccination is targeted, is unlikely to undergo significant change in the short- to medium-term.

The varicella vaccine, Varivax®, is currently licensed for use in the European Union, is marketed in Ireland and is therefore available to purchase privately. While it is understood that some parents have taken the decision to vaccinate their children at their own expense, the number of people in each of the model health states has not been adjusted to account for this. Data on the numbers that have been vaccinated by age group, the number of doses received and time since vaccination are not publicly available. In the absence of these detailed data, it was not possible to incorporate the impact of privately funded varicella vaccination in the model. As a result, baseline population immunity to varicella may be higher than that estimated, which in turn may impact the cost-effectiveness of a universal childhood varicella vaccination programme.

In terms of modelled disease states, individuals who recovered from herpes zoster were assumed to be permanently immune and remained in the $R_z$ compartment.

However, the risk of recurrence has been reported as ranging from 1% to 6%, with long-term follow-up studies (of greater than 15 years) reporting higher risk (5 to 6%).[162] Inclusion of recurrent herpes zoster would improve the cost-effectiveness of varicella vaccination but given the estimated annual number of cases and the effects of discounting over the 80 year time horizon of the model, it is unlikely that the overall result would change in any meaningful way.

An important aspect of the epidemiological model was the incorporation of contacts between individuals to simulate the spread of disease. Contacts between individuals were estimated based on the POLYMOD data for the UK.[135] The underlying 2006 study included a number of European countries, but did not include Ireland. Cultural, societal and demographic differences mean that the data may not be fully representative of social interactions in Ireland. However, the age profile of the UK in 2006 is similar to that in Ireland in 2022. Detailed contact matrix data are rare, and the POLYMOD data represent the best available data at present and were used to populate Irish SEIR models during the COVID-19 pandemic.[180] Given that the model provided an accurate estimate of varicella incidence in the 'no vaccination' scenario, the contact matrix is likely to be sufficiently accurate for application to the Irish population.

There are a number of aspects of the epidemiology of VZV infection that are not fully understood and therefore key model parameters are highly uncertain. Cell-mediated immunity is believed to play a key role in preventing VZV reactivation and the development of herpes zoster. In the epidemiological model, the duration of cell-mediated immunity governs the movement of individuals from the 'R' (recovered from varicella) disease state to the '$S_Z$' (susceptible to herpes zoster) disease state. In the review of economic modelling studies (chapter 6), parameter values used for the average duration of cell-mediated immunity varied considerably, from two years[132] to 113.5 years.[134] Cases of herpes zoster are observed in young children, indicating that the duration of cell-mediated immunity could be short. It should be noted that the duration of cell-mediated immunity governs herpes zoster incidence in tandem with a second parameter: the age-specific rate of VZV reactivation. Values for the latter parameter were derived through a calibration exercise. Adopting a longer duration of cell-mediated immunity would have resulted in higher rates of reactivation from the calibration exercise. We adopted a conservative approach and assumed a value of two years for the average duration of cell-mediated immunity. Additionally, the exogenous boosting theory is poorly understood, much debated and the magnitude of the effect, if it exists, is unknown.[140, 181] In the absence of conclusive evidence, our base case analysis excluded exogenous boosting and its potential impact was explored in a scenario analysis. When compared with no vaccination, the model including exogenous boosting predicted a small and temporary increase in recovered herpes zoster cases in the first 20 years of the

model in the five age groups from 15 to 19 years to 50 to 59 years inclusive for all three vaccination strategies. However, the one-dose strategy remained cost-effective, relative to no vaccination, at a WTP threshold of €20,000/QALY gained and the ICER for the two-dose long interval strategy, relative to the one-dose strategy, increased to €68,966/QALY gained.

In the absence of an indicated varicella vaccine price, a cost of €32.73 per vaccine dose was assumed in the economic analysis. This was based on an average of two varicella vaccine prices used in a CEA of varicella vaccination for the UK.[132] The sensitivity analysis conducted for both the CUA and BIA highlight the impact of the uncertainty associated with the vaccine cost. When the vaccine cost was set at 20% above the base case value, the one-dose strategy remained cost-effective at a willingness to pay threshold of €20,000/QALY gained. However, the five year budget impact was particularly sensitive to this increase in the vaccine cost. A 20% increase in the vaccine cost resulted in a 17.1% increase in the budget impact for the one-dose strategy compared with the base case scenario. The corresponding increases in the budget impact for the two-dose long and short interval strategies were 16.8% and 15.5% respectively.

In the economic model, health outcomes associated with varicella were limited to non-severe disease and severe disease requiring hospitalisation. Complications potentially arising from initial varicella infection, including severe complications such as invasive Group A streptococcus (iGAS) infections, are not easily analysed using routinely available data and therefore have not been included in the model. It is likely that the cost-effectiveness of vaccination is under-estimated when outcomes relating to severe complications associated with varicella are excluded. However, given the small number of potential number of cases involved, it is unlikely that this would impact the overall results of the economic evaluation. The outcomes associated with herpes zoster were limited to acute disease, severe disease requiring hospitalisation, and post herpetic neuralgia. While it is acknowledged that herpes zoster can also be complicated by other serious neurological and ocular disorders,[182, 183] post herpetic neuralgia was included in the economic analysis as the most common complication. Additionally, disease outcomes for both varicella and herpes zoster did not include death. While death from varicella can occur, it is extremely rare. Since 2012, only one notified hospitalised case in Ireland was reported as having died; this case was in the 55 to 64 year old age group, but the cause of death was recorded on Computerised Infectious Disease Reporting system as “not known”.[70] Case fatality rates of 61 per 100,000 cases (0.061%) in those aged ≥65 years and two per 100,000 cases (0.002%) in those aged 45-65 years have been reported for herpes zoster.[77] Based on our base case model estimates which predict a 50% decrease in the number of herpes zoster cases at year 80, the number of deaths avoided over the lifetime of the model is not expected to exceed

170. The inclusion of death due to varicella and herpes zoster would improve the cost-effectiveness of varicella vaccination, however the estimated number of deaths avoided it is unlikely to impact the overall results.

While PSA is the preferred approach for exploring uncertainty arising from parameter imprecision,[139] a full PSA of all model input parameters was not possible. Similarly, in the case of the univariate sensitivity analysis, it was not possible to vary each model input parameter. Some of the epidemiological model inputs (for example, probability of VZV infection given contact and herpes zoster reactivation rates) are calibrated to disease incidence data and variations in the parameters may result in distortion of modelled disease transmission and unreliable disease outcome data. Additionally, the completion time for one run of the epidemiological model ranged from 20 minutes to two and half hours, limiting the scope for sensitivity analysis.

### 7.5.3 Conclusions

From the payer perspective, the one-dose universal varicella vaccination programme was cost-effective in reducing incidence of varicella disease when compared with no vaccination. However, model results suggest that the incidence of disease remains high with a one-dose strategy, relative to two-dose vaccination strategies, due to lower vaccine effectiveness and waning of immunity with a single vaccine dose. While the two-dose strategies were far more effective in reducing incidence of varicella disease and estimated ICERs were similar, relative to a one-dose strategy, there is considerable uncertainty with regard to their cost-effectiveness at a WTP threshold of €45,000/QALY gained. From a societal perspective, all three vaccination strategies dominate the no vaccination scenario, being less costly and more effective, with the two-dose short interval strategy dominant over all others. In terms of budget impact, the one-dose strategy was the least costly (€13.1 million) over a five year time period. The incremental cost of the two-dose long interval and two-dose short interval strategies were €16.1 million and €28.1 million, respectively. The lower budget impact for the two-dose long interval strategy reflects the fact that only one birth cohort will complete the two-dose schedule within the five year time horizon of the BIA.

# 8 Organisational issues

## Key points

- Each of the three varicella vaccination regimens would give rise to different organisational implications:
    - A one-dose regimen would take place as part of the existing childhood immunisation programme. It may result in the 12 month visit being prolonged by the addition of varicella vaccination.
    - A two-dose short interval regimen would leverage off the existing 12 month GP visit and also create a new immunisation visit at 15 months. This regimen would therefore require an additional GP visit, placing a burden on primary care as well as parents and guardians.
    - A two-dose long interval regimen would leverage off the existing 12 month GP visit and the schools-based immunisation visit for four to five year olds but in both instances may result in additional time required for vaccination.
- An information campaign for parents would be an important component of any change to the national immunisation schedule, to educate parents, 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 childhood vaccines as part of the immunisation programme.

## 8.1 Introduction

The aim of this chapter is to provide an overview of the potential organisational issues associated with the addition of varicella vaccination to the routine childhood immunisation schedule in Ireland.

## 8.2 Current childhood immunisation schedule

Ireland has a nationally funded childhood immunisation programme that commenced in the 1930s. The programme currently includes the primary childhood immunisation

programme for children aged two to 13 months inclusive, which is administered by GP practices, and the Schools Immunisation Programme (SIP) which provides vaccinations for school-age children in junior infants and students in first year of secondary school (Table 8.1). [184] Immunisations at the GP practice require five visits, and are administered by a GP or practice nurse. If vaccinations are administered by nurse vaccinators, a GP must be present in the building while vaccines are being given, and for 15 minutes after the last vaccine is administered to deal with anaphylaxis or any other adverse events that might occur.[185] The HSE school vaccination teams, comprising doctors and nurses, administer vaccines to children at school under the SIP. In Sligo, Leitrim and Donegal, children in junior infants receive the 4 in 1 (diphtheria, polio, tetanus and whooping cough [pertussis]) booster vaccine and second dose of the MMR vaccine from their GP instead of at school.[186]

### Table 8.1 Recommended childhood immunisation schedule in Ireland 2020

| Age / School class | Vaccinations | Setting | Number of Vaccinations |
|---|---|---|---|
| 2 Months | 6 in 1 (DTaP/Hib/IPV/Hep B) | Primary care | 3 injections + 1 oral |
| | PCV | | |
| | MenB | | |
| | Rotavirus | | |
| 4 Months | 6 in 1 (DTaP/Hib/IPV/Hep B) | Primary care | 2 injections + 1 oral |
| | MenB | | |
| | Rotavirus | | |
| 6 Months | 6 in 1 (DTaP/Hib/IPV/Hep B) | Primary care | 3 injections |
| | PCV | | |
| | MenC | | |
| 12 Months | MMR | Primary care | 2 injections |
| | MenB | | |
| 13 Months | Hib/MenC | Primary care | 2 injections |
| | PCV | | |
| Junior Infants (4/5 Years) | 4 in 1 (DTaP/IPV*) | Primary school | 2 injections |
| | MMR | | |
| 12-13 Years | HPV (2 doses 6mths apart) | Secondary school | 4 injections |
| | Tdap | | |
| | MenACWY | | |

**Source:** Health Service Executive. Immunisation Guidelines. Chapter 2 General Immunisation Procedures. Dublin: HSE National immunisation Office; 2021.
*dTap/IPV can be given if DTaP/IPV is not available
**Key:** DTaP - diphtheria, tetanus and acellular pertussis; HepB - hepatitis B; Hib - haemophilius influenzae b; HPV - human papilloma virus; IPV - inactivated polio virus; MenACWY - meningococcal ACWY; MenB - meningococcal B; MenC - meningococcal C; MMR - measles, mumps and rubella; PCV - pneumococcal conjugate vaccine; Tdap - tetanus, low-dose diphtheria and low-dose acellular pertussis

The childhood immunisation schedule is coordinated by the National Immunisation Office (NIO).[187] 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.[187] 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.

## 8.3 Estimated number of eligible children

Based on the total number of births in Ireland in 2021, the estimated eligible population for varicella vaccination would be approximately 60,000 children per annum. However, it is important to note that the number of births is subject to variability and trends. There was a peak in births of 75,554 in 2009 followed by a gradual decline. These shifts reflect the changing age profile of the general population and trends in fertility.[188] Over the longer-term, it can be anticipated that the eligible population will vary between 55,000 and 75,000.

## 8.4 Addition of varicella to the childhood immunisation schedule

Several vaccination dosage regimens are under consideration by decision makers in Ireland, with each option having slightly different organisational implications. We have considered the organisational implications of the three dosage regimens that are included in the economic assessment (chapter 7):

- one dose at 12 months
- two doses with the first dose at 12 months and second dose at 15 months
- two doses with the first dose at 12 months and second dose at four or five years.

Additionally there is the potential that a quadrivalent (measles, mumps, rubella, varicella [MMRV]) vaccine may be offered for the second dose as part of the third regimen. Each regimen has different organisational implications that should be considered.

### 8.4.1 Regimen option one: one dose at 12 months

In this first regimen children would be offered one dose of the varicella vaccine at 12 months. The varicella vaccine would be given alongside the two vaccines administered at 12 months of age in the current schedule: measles mumps and rubella (MMR) (dose one), and meningococcal B. As this is an established visit to the GP, the implications are limited to the immunisation visit potentially taking longer.

However, it is more efficient to leverage off an existing visit than to implement a new visit.

Vaccination invitation letters are sent to parents by local health offices as a reminder to bring babies to GP practices for vaccination.[189] Parents who are late bringing their baby for vaccination are sent a reminder letter.

As outlined in chapter two, the Meningococcal serogroup B (MenB) vaccine is not listed as one of the vaccines that may be co-administered with Varivax® and ProQuad®.[18, 19] Co-administration at 12 months is likely with all regimens evaluated in this HTA, so clinical consideration should be given to this issue. Chapter two also indicated that separate vaccinations could be considered, when possible, for Priorix-Tetra® and Bexsero® (Meningococcal serogroup B [MenB] vaccine), due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when co-administered.[20] Bexsero® is currently administered at 12 months, and so this could prohibit the use of the quadrivalent Priorix-Tetra® vaccine at this time point.

### 8.4.2 Regimen option two: two doses with the first dose at 12 months and second dose at 15 months

In the second regimen under consideration, the first dose of varicella vaccine would be administered as outlined for regimen one. The second dose would be administered at 15 months of age and, as outlined in Table 8.1, no other vaccines are currently scheduled at this time. Therefore, an additional GP visit would be required. 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.[190] Increasing the number of GP visits required for childhood immunisation could 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. However, it should also be noted that the vaccine can be administered by a practice nurse and that it should represent a minor increase in workload in any single practice. As it is based on the age of the child, the workload is distributed across the year rather than being concentrated at a particular time of year, as can happen in the schools-based programmes. An additional immunisation visit to the GP also potentially creates the need for some parents or guardians to take time off work to bring their child to the GP.

### 8.4.3 Regimen option three: two doses with the first dose at 12 months and second dose at 4 or 5 years

In the third regimen under consideration, the first dose of varicella vaccine would be administered as outlined for regimens one and two. The second dose would be given at age four or five in junior infants as part of the SIP.

The SIP was developed in accordance with the guidance issued by the National Immunisation Advisory Committee (NIAC) of the Royal College of Physicians of Ireland, and contained in the Immunisation Guidelines for Ireland. The SIP is carried out by staff from each Community Healthcare Organisation (CHO) area.[191]

The Department of Health Immunisation Policy for the SIP, supported by the Department of Education, states that the 4 in 1 and MMR vaccines should be delivered on primary school premises, and the funding provided to CHOs is on the basis that the programme is primarily provided on school premises with catch-up clinics provided in Local Health Centres.[191] Students attending special schools and those home schooled may be vaccinated at school or at a HSE clinic.

In Sligo, Leitrim and Donegal, children aged four to five years receive the 4 in 1 (diphtheria, polio, tetanus and whooping cough [pertussis]) booster vaccine and second dose of the MMR vaccine from their GP instead of at school. Similarly, it is expected that children in these counties would receive the second varicella vaccine dose at four to five years of age from their GP.[186] This may increase the burden on GPs in those counties although it would be in the context of an existing immunisation visit.

The NIO sends information packs to each CHO each year and the CHO sends these to schools as soon as the school year starts for immediate distribution to parents and legal guardians. NIO guidance states that parents should not be routinely invited to attend school vaccinations.[191] There is no requirement to have a parent present at the time of vaccination and if there is a valid consent form from parents, all children should be vaccinated regardless of whether a parent is present or not.

Currently, students being home schooled are required to register with TUSLA, however registration is not required before age six years or after age 18 years.[191] TUSLA informs the NIO of the number of home schooled children in the ages eligible for vaccination and the NIO issues immunisation packs to TUSLA for onward distribution to parents. The cover letter advises parents/legal guardians/students to contact immunisation staff at their HSE Area to arrange vaccination. When the parent/legal guardian/student contacts their HSE Area they should be given an appointment to attend a school clinic or mop up clinic. It is anticipated that these arrangements would also apply for varicella vaccination.

Children should be given the MMR vaccine in the right deltoid and DTaP/IPV vaccine in the left deltoid.[191] Similar guidance should also be given for administration of the varicella vaccine as this will enable local reactions (for example, pain, redness and swelling at the injection site) to be attributed to the correct vaccine in the event of a report of an adverse reaction. If the quadrivalent MMRV vaccine was offered for the second dose, the organisational issues for the second dose in regimen option three would be minimised.

Guidelines for school immunisation staff detailing these arrangements are published annually by the HSE.

As outlined in chapter two, concurrent administration of Varivax® with tetravalent, pentavalent or hexavalent (diphtheria, tetanus, and acellular pertussis [DTaP])-based vaccines has not been evaluated.[19] This would need consideration if the second dose of the varicella vaccine is scheduled at four or five years of age.

## 8.5 Resources

An expansion of the childhood immunisation schedule in Ireland to include varicella vaccination would have resource implications at the organisational level within the health service as a whole. The budget impact analysis (BIA) (chapter 7) aimed to capture these resource implications over the short term and estimate the incremental costs to the health service of adding varicella vaccination to the childhood schedule. It included organisational costs associated with vaccine administration for both GP practices and the SIP, the cold chain service and education and communication about the programme, as well costs averted due to a reduction in hospitalisations for varicella.

### 8.5.1 Staff

Inclusion of varicella vaccination in the childhood immunisation schedule may require additional staff in certain circumstances. If an additional GP visit is necessary (regimen option two), resources might be redeployed from other practice activities and require backfill. Administration of an additional vaccine at an existing appointment may also place an additional burden on the GP practice or schools immunisation 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. As already noted, where the varicella vaccine is administered as part of an existing immunisation visit, the logistical burden should be relatively minor.

In chapter 7, it was estimated that childhood varicella vaccination would result in a reduction of up to 71% (two-dose short interval regimen) in varicella cases over the

80 year time horizon of the model. Given the estimated reduction in the number of cases, over time there should be an evident decrease in GP consultation rates and the number of hospitalisations for varicella, relieving a significant amount of the current burden on the health system due to varicella.

It should be acknowledged that varicella vaccination may give rise to some minor adverse reactions. While it is not anticipated that this will result in additional primary care visits, it cannot be ruled out that some parents may bring their child to the GP for assessment. It must be borne in mind that where the varicella vaccine is administered alongside other vaccines, it may be challenging to determine which vaccine adverse events are associated with.

### 8.5.2 Vaccine storage and handling

All varicella vaccines would be 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 primary childhood schedule and schools during the 2022/23 academic year.[191] Cold chain procedures must also be followed.[191] An estimated cost for the varicella vaccine cold chain service has been included in the BIA. The NIO is responsible for managing vaccine procurement and distribution, developing training and communication materials for health professionals and the general public.[187]

### 8.5.3 Information and awareness

*Public awareness campaign to support rollout*

All information materials for the general public are developed and distributed by the NIO who also manage the national immunisation website www.immunisation.ie.[187]

An information campaign for parents would be an important component of any change to the national immunisation schedule, to educate parents, 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 childhood vaccines as part of the immunisation programme. An estimated cost for education and communication has been included in the BIA.

*Training*

Each vaccinator in the SIP must be familiar with techniques for resuscitation of a patient with anaphylaxis and have completed a Basic Life Support training course within two years.[191] Each vaccinator should be familiar with the "Anaphylactic

Reactions: Treatment in the Community" protocol, in the Immunisation Guidelines for Ireland.[192]

## 8.6 Anticipated vaccine uptake

The WHO stipulates that the sustained vaccination coverage of at least 80% is needed to maintain herd immunity against varicella.[5] A UK cross-sectional study published in 2023, found that 74.0% of parents were extremely or somewhat likely to accept a varicella vaccine for their child if one became available.[193] A Swedish study found that 85% of parents would be highly likely to vaccinate their child if it was introduced into the national programme.[194] In the USA, single dose varicella vaccination has been recommended since 1995 and two dose vaccination recommended since 2007. Vaccination coverage rates are reported to be 90% to 91% since 2007 for one dose among children aged 19 to 35 months and at least 85% for two doses among adolescents aged 13 to 17 years without a history of varicella since 2016.[195] For the year 2020/21, overall national coverage was reported to be 93.6% for the varicella vaccine in the USA, adhering to the individual state recommendations for either one or two doses.[196]

Based on these estimates, and considering the ≥80% coverage recommendation from the WHO, we would anticipate at least 46,800, or 80% of the eligible cohort children per year would avail of varicella vaccination. If a two-dose regimen is chosen this would require at least 93,600 doses of the vaccine. If a two-dose long interval regimen is chosen, resources would be lower in the first four years of the programme compared with the two-dose short interval regimen, as cohorts would only be eligible for the first dose in these years.

### 8.6.1 Programme monitoring and evaluation

Since 2000, the Health Protection Surveillance Centre (HSPC) has collated data and reports on the uptake of vaccines provided through the childhood immunisation schedule.[151] The HSPC reports quarterly on vaccination uptake rates. If varicella vaccination is added to the national schedule it will be incorporated into the same surveillance system. As the vaccination coverage threshold to achieve herd immunity against varicella is specified to be ≥80% by the WHO,[5] regular evaluation of varicella vaccination uptake rates should be undertaken to monitor against coverage targets.

## 8.7 Discussion

Ireland has a nationally funded childhood immunisation programme that commenced in the 1930s. It is assumed that where possible, varicella vaccination would be

incorporated into the existing immunisation programme and therefore the anticipated organisational issues are relatively minor.

The identified organisational issues differed across the three evaluated regimens. The biggest organisational issue identified was with regimen option two: two-dose short interval, with the first dose administered at 12 months and second dose at 15 months. In the current immunisation schedule there is no GP visit at 15 months. Therefore the addition of varicella vaccination to the immunisation schedule with this regimen would require an additional GP visit for the annual birth cohort, placing an additional burden on primary care and also on parents and guardians. Over the longer term, this will be partly offset by a reduced need for primary care visits associated with varicella.

An expansion of the childhood immunisation schedule in Ireland to include varicella vaccination would have resource implications at the organisational level within the health service as a whole, as captured by the budget impact analysis (BIA) (chapter 7).

An information campaign for parents would be an important component of any change to the national immunisation schedule, to educate parents, allay any concerns regarding the safety or efficacy of the vaccine, and to 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 childhood vaccines as part of the immunisation programme.

# 9 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 varicella vaccination is very effective at reducing incidence and the risk of severe disease.
- Almost everyone who is not vaccinated will contract varicella over their lifetime, the majority before the age of ten years. The lifetime risk of developing herpes zoster is approximately 30%. As such, and unusually for an immunisation programme, most people who get vaccinated will personally benefit through avoiding infection.
- The varicella vaccine is considered safe. While mild local and systemic reactions, such as fever and rash, are relatively common, serious adverse events are rare.
- Given that the vaccine is administered to children, it is the responsibility of parents and guardians to provide informed consent. It is important that in giving consent, parents and guardians fully understand the benefits and harms of vaccination.
- If a high proportion of eligible children avail of vaccination, it will confer some degree of herd immunity. Such protection may be particularly beneficial for those who are immunocompromised and therefore contraindicated for the vaccine.
- Policy makers have a duty to ensure resources are allocated fairly. Reallocation of resources has the potential to affect the existing health care system as it may divert resources from other effective treatments provided within the overall healthcare fund. The introduction of varicella immunisation will create demand for primary care resources which could result in displaced care. However, over time it will lead to a shift in demand from treatment to preventive care.

## 9.1 Introduction

This chapter discusses the ethical issues that should be considered in relation to the expansion of the childhood immunisation schedule to include varicella vaccination. This chapter was broadly developed in line with the structure described in the

European network of HTA (EUnetHTA) Core Model.[197] The ethical issues raised around a technology must be assessed in relation to the prevalent social and moral norms relevant to the technology. 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 prevent or reduce the spread of infectious disease through vaccination of the population. 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 must 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 a varicella immunisation programme aimed at children aged 12 months to five years inclusive. In order for a child to receive a vaccine, informed consent must be provided by a parent or guardian. For simplicity, parents are referred to in the subsequent text, but this also includes guardians.

Several vaccination dosage regimens are under consideration by decision makers in Ireland, with each option having slightly different ethical implications. We have considered the ethical implications of the three dosage regimens that are included in the economic assessment (chapter 7): i) one dose at 12 months, ii) two doses with the first dose at 12 months and second dose at 15 months, and iii) two doses with the first dose at 12 months and second dose at five years. Additionally there is the potential that a quadrivalent (Measles, Mumps, Rubella, Varicella [MMRV]) vaccine may be offered for the second dose as part of the third regimen.

## 9.2 Benefit harm balance

Varicella is a common, acute and highly contagious disease mainly affecting children. The average incubation period for varicella is 14 to 16 days following exposure to an infectious individual with varicella or herpes zoster.[40] It may begin with cold-like symptoms, followed by a high temperature, and is characterised by a pruritic (itchy), blister-like rash, mostly on the face and torso, typically lasting four to seven days.[4] Most children will develop varicella before their tenth birthday (see chapter 3). While varicella is typically a childhood illness, it can and does affect adults. Varicella is often more severe in adults than children, with complications also more common. Although a significant proportion of women will have had varicella as a child,

varicella is estimated to cause complications in approximately three in every 1,000 pregnancies.[46]

The burden of disease associated with varicella can be considered through GP attendance and hospitalisations. GP attendance rates are highest among those aged under five, with consultation rates falling with increasing age.[53, 54]The annual incidence rate of varicella-related hospital admissions in Ireland was estimated at 4.9 per 100,000 population.[57] Infants and young children comprised the majority of admissions; 47% were less than three years old and 76% were less than 10 years old.[57] While death due to varicella is rare, it can and does occur.[70]

Primary infection with the varicella zoster virus results in varicella, after which the virus becomes latent in the body's nervous system. The virus may reactivate after a period, sometimes several decades later, resulting in herpes zoster (shingles). Herpes zoster usually starts with pain in the area of the nerve which is affected, followed by the development of a painful rash, usually affecting one side of the face or body.[4] The lifetime risk of developing herpes zoster is approximately 30%,[74] and 50% in people aged 85 years and over.[35] Morbidity associated with herpes zoster increases with age and the most common complication is post herpetic neuralgia (PHN). Those with PHN experience persistent pain (for more than 90 days after onset) in the area of the rash with the potential to cause significant reductions in quality of life, activity, mood and sleep.[76]

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 a highly infectious disease like varicella, where most 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.

### 9.2.1 Benefits and harms at an individual level

Since the development of the varicella vaccine in the 1970s and the subsequent introduction of universal childhood varicella vaccination programmes, starting with the USA in the 1990s, numerous studies have been undertaken to determine the efficacy and effectiveness of the varicella vaccine. The evidence generated by those studies was reviewed in chapter 4. A wealth of data has also been gathered in relation to the safety of the vaccine, including following the roll-out of a number of national varicella immunisation programmes. This evidence was reviewed in chapter

5. In this section, the benefit-harm balance is considered from an ethical perspective.

### 9.2.2 Benefits

An overview of systematic reviews of varicella vaccine efficacy and effectiveness 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 incidence of varicella. The evidence suggests that two-dose strategies are more efficacious/effective than one-dose strategies in preventing varicella of any severity, but that one- and two-dose strategies have similar high efficacy/effectiveness in preventing moderate or severe varicella. The evidence also suggests that one-dose strategies may be less effective in outbreak settings, but this may not be the case for two-dose strategies. Additionally, although evidence was limited with respect to two-dose strategies, there appears to be greater waning of immunity following one-dose than two-dose schedules.

Given the difference in efficacy in one-dose versus two-dose strategies, particularly with regard to varicella breakthrough, it is possible that the one-dose regimen may shift varicella infection to older ages in some settings. This is a risk because varicella can be more severe for older children and adults.[198]

The HSE advises that children with varicella should stay home from school, pre-school or childcare until their spots are dry which is usually five to seven days after they first appear.[199] Therefore the introduction of a varicella vaccination programme would benefit children through fewer missed days of school.

### 9.2.3 Harms

An overview of systematic reviews of varicella vaccine safety was carried out as part of this HTA and is fully reported in chapter 5. The evidence suggests that both monovalent and quadrivalent varicella vaccination are safe. While mild local and systemic reactions, such as fever and rash, are relatively common, serious adverse events are rare. Febrile seizures are possible adverse effects of both the monovalent and quadrivalent MMRV vaccine. The limited evidence on the co-administration of the varicella vaccine with other vaccines suggests that co-administration does not compromise the safety of the vaccines. In the absence of natural infection with wild-type varicella, development of vaccine strain varicella is iatrogenic. However, the risk of healthy, vaccinated people transmitting vaccine strain varicella to contacts is considered minimal and only if a rash is present, with resulting secondary cases of varicella typically mild.[113]

Parents must provide consent for administration of the vaccine, and as such are responsible for deciding whether or not it is acceptable to expose their child 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 parents 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 parent who believes they have exposed their child to harm through vaccination. The concerns of parents 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 parents to have caused harm, these concerns are not dismissed. It is imperative to acknowledge the fact that parents who believe their child was harmed through vaccination are not inherently opposed to vaccination, as they consented to receiving the vaccine in the first place.

As outlined in section 9.2.2, children with varicella infection likely miss at least five days of day care, preschool or school. If varicella vaccination is not introduced, then most children will have missed at least one week of childcare, preschool, or school by the time they are ten. A small proportion of these may develop severe complications which can result in hospitalisation (see chapter 3). These outcomes may be considered as harms of not introducing a varicella immunisation programme. Equally, it must be considered whether parents may consent to vaccination of their child not to avoid ill-health in their child so much as to eliminate the need to take time off work.

### 9.2.4 Perceptions and expectations of varicella vaccination

The evaluation team were not able to identify Irish data on the perception of parents towards varicella vaccination. However, it should be noted that parents in Ireland do pay privately for their children to receive the varicella vaccine indicating that there is a baseline level of acceptance. Data on varicella vaccine sales do not provide any information on the age of vaccine recipients or the number of doses given.

A Swedish cross-sectional study conducted while varicella was being reviewed for inclusion in the Swedish Public Health Agency's national immunisation programme

found that 85% of parents would be highly likely to vaccinate their child if it was introduced into the national programme.[194] However, the study also found statistically significant differences in awareness and behaviours between sociodemographic subgroups. Respondents from metropolitan areas, those with university degrees and respondents with a higher income were more likely to be aware of the varicella vaccine and to have vaccinated their child. In a UK cross-sectional study published in 2023, 74.0% of parents were reportedly extremely or somewhat likely to accept a varicella vaccine for their child if one became available.[193]

A study from the USA published in 2000 found that typically parents felt that the vaccine was worthwhile even if the only benefit was preventing a rare complication.[200] However, the majority of parents disagreed that vaccination was worthwhile if the only benefit was preventing lost time from work, and that the vaccine was worthwhile even if immunity was not lifelong.

The latest immunisation uptake rates in children 24 months of age in Ireland are from quarter three 2022 and ranged from 83.1% for the Meningococcal group C vaccine to 93.0% for the 6-in-1 vaccine.[151] These figures indicate a high level of acceptance of the existing childhood immunisation programme.

### 9.2.5 Benefits and harms at a population level

#### 9.2.5.1 Herd immunity

Herd immunity occurs when circulation of a pathogen is significantly curtailed in a community because most of the people it encounters are immune.[201] Immunity is conferred by immunisation and the more people that are vaccinated, the more those who are not vaccinated are indirectly protected because the high immunisation rate stops the virus transmission.[201, 202] The infectiousness of the pathogen and the effectiveness of the vaccine determine the threshold for herd immunity for any disease.[202]

The vaccination coverage threshold to achieve herd immunity against varicella is specified to be ≥80% by the World Health Organization (WHO).[5] The WHO advises that the introduction of routine childhood varicella vaccination should be considered in countries where varicella is an important public health burden and resources are sufficient to ensure sustained vaccination coverage of at least 80%.[5] Similarly, the European Centre for Disease Prevention and Control (ECDC) recommends that in considering the introduction of a varicella immunisation programme, individual countries should assess both their epidemiological and socioeconomic situations and their capacity to achieve high vaccination coverage.[1]

According to the WHO, if vaccine coverage remains <80% over the long term it is expected to shift varicella infection to older ages in some settings. This is a risk because varicella can be more severe for older children and adults.[198]

Vaccination is often used as a mechanism to achieve benefits for the greater good, and many individuals experience a minor burden for the few who will experience a substantial benefit. In the case of varicella vaccination, the incidence of varicella is relatively high, and hence a large proportion of the population will experience some form of benefit, either directly or through a family member not contracting the disease. There will be a benefit for those adults who have not yet contracted varicella (approximately 5 to 10% - chapter 3), particularly pregnant women. Herd immunity will also benefit those who are immunocompromised and therefore ineligible for the vaccine (section 9.5).

It should be borne in mind that the concept of herd immunity does not hold for unvaccinated individuals that move out of the vaccinated population. For example, if an unvaccinated individual moves to a country with no varicella vaccination, then they will no longer benefit from herd immunity.

#### 9.2.5.2 Impact on incidence of herpes zoster

In their position statement on varicella vaccination, the WHO stipulates that decision-making on childhood varicella vaccination should also include consideration of the possible impact on incidence of herpes zoster.[5]

Primary infection with VZV results in varicella, after which the virus lies dormant in the nervous system. The virus may reactivate after a period, sometimes several decades later, resulting in herpes zoster. Varicella vaccination should therefore reduce the incidence of herpes zoster over time as there will be a diminishing number of people that have experienced primary infection with VZV. Routine varicella vaccination was introduced in the US in 1995. Long-term data from the US show a lower risk for herpes zoster among children, and at the population level the lower risk is reflected in stepwise declines in herpes zoster incidence as age groups became dominated by vaccinated persons.[203]

The exogenous boosting hypothesis proposes that re-exposure to circulating VZV over a person's life span inhibits reactivation of the virus, and consequently a person may be less likely to develop herpes zoster.[142] In considering the impact of varicella vaccination on herpes zoster, one should therefore consider the exogenous boosting hypothesis. There is much inconclusive evidence about whether the hypothesis has been proven or not, and if it exists, to what extent does it impact incidence of herpes zoster.[142] It is very difficult to make the causal link to prove the exogenous boosting hypothesis due to substantial confounding factors over a lengthy time

period. If the exogenous boosting hypothesis holds, and the varicella vaccine was to be introduced, the possible benefit from exogenous boosting would diminish, potentially resulting in increased incidence of herpes zoster among those not vaccinated against varicella.

Two countries have reported that they have not included varicella in their childhood vaccination programme due in part to the results of mathematical modelling that assessed the impact of such a programme on the incidence of herpes zoster due to the exogenous boosting hypothesis. In Norway, varicella vaccination is not currently included in the national childhood immunisation programme.[204] A programme of research was undertaken to investigate the impact of varicella vaccination on incidence of herpes zoster, with an aim to support national vaccine policy decisions.[205] Universal varicella vaccination was predicted to result in a large increase in incidence of herpes zoster over the medium term.[206] In 2016 the Joint Committee on Vaccination and Immunisation (JCVI) in the UK did not recommend universal varicella vaccination as economic modelling showed that varicella vaccination was not cost-effective, largely because of a predicted increase in herpes zoster incidence due to a reduction in immunological “boosting” from circulating varicella virus.[207] More recently (June 2022), the JCVI reported that varicella vaccine modelling work is being updated to include new research on both the quality of life impact of varicella on children and families and IgG seroprevalence and to incorporate experience data from 25 years of universal childhood varicella vaccination in the US, including the dynamics of exogenous boosting.[208]

The long-term data on routine varicella vaccination from the US show that the predicted increase in herpes zoster among adults based on the exogenous boosting theory was not observed. While herpes zoster is more common in adults, the US data also show a pattern of decline in the incidence of herpes zoster in children that provides expectation that overall rates of herpes zoster will decline as vaccinated children age.[203]

As stated previously, it is difficult to quantify the possible effect or prove the validity of the exogenous boosting hypothesis. Data from the US suggests that the impact of exogenous boosting on incidence of herpes zoster is not as significant as previously thought. According to Luyten et al. the exogenous boosting effect on herpes zoster for elderly people is much more uncertain than the direct protective effects of vaccination on chickenpox in children.[209]

The lifetime risk of developing herpes zoster is approximately 30%,[74] and 50% in people aged 85 years and over.[35] A herpes zoster vaccine is commercially available and, assuming the exogenous boosting hypothesis holds, a vaccination programme for adults could potentially negate some of the possible impact of a varicella vaccination programme on incidence of herpes zoster in adults.

#### 9.2.5.3 Impact on existing national immunisation programme

The purpose of this HTA is to examine the impact of adding routine varicella vaccination to the national childhood immunisation programme. There are two ethical issues relevant to the current national immunisation programme: whether the addition of the varicella vaccine would compromise the public perception of the programme, and specifically the potential administration of the varicella vaccine as part of a quadrivalent MMRV vaccine.

The current national childhood immunisation programme targets disease with serious symptoms and outcomes including death.[210] While varicella can result in complications and death, these events are extremely rare (chapter 3). Among the general public, chickenpox may be considered a rite of passage for young children, where they typically develop mild symptoms and acquire lifelong immunity. Anecdotal reports suggest that some parents may intentionally expose their children to other children presenting with varicella. This practice of deliberate infection is influenced by the understanding that it is generally known that varicella is milder in younger people and that controlled exposure enables choosing the timing of infection. If varicella is generally viewed as a mild disease, adding varicella vaccination to the childhood schedule may have implications for the existing national immunisation programme. If some consider varicella a less serious disease this could lead to a perception that obtaining childhood vaccines is unimportant, thereby undermining the existing programme. According to Vanderslott, parents may fear that multiple vaccines 'overload' a child's immune system even though there is no scientific basis for this view.[211] The tolerance of parents for the inclusion of vaccinations for milder diseases, as part of an increasing number of vaccines recommended, may affect their adherence to national immunisation schedules.[211] According to Pierik, national immunisation programmes cannot be expanded indefinitely; there is a finite number of vaccines which can be included after which the legitimacy of the programme as a whole is undermined.[198] In a survey on the acceptance of varicella vaccination in France and Germany for parents who were reluctant to allow their children to receive the vaccine, the two main reasons for their reluctance were similar in the two countries, 'complications following vaccination' and 'too many vaccinations'.[212] A UK study published in 2023 found that although parents have a preference for their child having fewer injections, many parents would still accept a varicella vaccine even if this required an additional injection.[193] Pierik also suggests that once the limit has been reached, adding vaccines to the schedule would undercut the vaccination rate of vaccines that were on the schedule prior to the addition.[198] The WHO advises that the vaccination rate for measles must be as high as 95% to ensure complete suppression of the disease, therefore any potential threat to achieving this level of coverage must be seriously considered.[213] It is also possible that parents may consider the varicella vaccination

worthwhile because varicella is extremely common, most children will likely get it, and that vaccination can prevent this.

A 2022 CDC report showed national coverage in the USA was 93.9% for two doses of measles, mumps, and rubella (MMR) vaccine and 93.6% for the varicella vaccine.[196] A repeated cross-sectional observational analysis from Philadelphia, USA also showed similar acceptance of the immunisation programme.[214]

For one of the dosage regimens under consideration, the varicella vaccine may be administered as part of the quadrivalent MMRV vaccine. If the varicella vaccine is administered with the MMR vaccine as part of the quadrivalent MMRV vaccine, this could have implications for coverage. If some people feel that varicella vaccination is unimportant, and do not opt for vaccination, this could lead to a corresponding decline in MMR vaccination rates. Conversely, if parents are hesitant to give the MMR vaccination to children this could impact varicella vaccination rates. It is also possible that some parents might want their children to receive the varicella vaccine but not the MMR vaccine or vice versa. It is unclear if this would be possible if the quadrivalent MMRV vaccine was part of a two-dose regimen. A decline in vaccination uptake or low uptake would potentially result in increased circulation of disease.

For one of the two-dose regimens under consideration, the first dose would be administered at 12 months and the second dose at five years. This is a large window of time which could allow for the emergence of breakthrough varicella. According to the CDC, prior history of varicella is not a contraindication to varicella vaccination, so when in doubt as to history, the vaccine should be administered.[195] In the USA, children with a clinician-diagnosed or verified history of typical varicella can be assumed to be immune to varicella and will not need to be vaccinated.[195] In Ireland, the majority of children who have varicella are treated at home and therefore have no verified history of varicella as they do not attend a GP appointment. Therefore it is likely that those individuals who have a breakthrough varicella infection between the first and second dose, will be expected to receive the second dose in Ireland. This could have an impact on vaccine coverage rates and vaccine hesitancy as if a child has had varicella, a parent might be reluctant to vaccinate. This also has implications if the second dose is administered as part of the quadrivalent MMRV vaccine.

Based on the current immunisation schedule, one of the dosage regimens under consideration (first dose at 12 months and second dose at 15 months) would require an additional visit to the GP. This could 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.

#### 9.2.5.4 Wider societal impact and caregiver burden

Attending vaccination appointments with children requires a time commitment from parents. If a two-dose short interval (first dose at 12 months and second dose at 15 months) regimen is selected, there may be an additional vaccination appointment required, which will add to the burden on parents. However, this inconvenience can be counterbalanced by the fact that once vaccinated, a child is unlikely to contract varicella and therefore parents will not need to forego other activities (such as work) to mind their sick child. HSE recommendations mean a child will likely spend at least five to seven days away from childcare facilities or school.[199] Based on incidence rates outlined in chapter 3, there is expected to be in the region of 60,000 annual cases of varicella in those aged less than 10 years. It is difficult to translate this to approximate work days lost as the caregiver burden might not fall to a working parent and siblings may contract the virus at the same time, however, the loss of productivity is still expected to be large. In the economic evaluation it was estimated that from the societal perspective, varicella vaccination was cost-saving relative to no vaccination. This finding was driven by the substantial productivity losses associated with parents and guardians taking time of work to care for children with varicella. Those productivity losses do not accrue to the State, but rather to businesses and individuals, and hence were not incorporated into the payer perspective.

## 9.3 Autonomy

### 9.3.1 Autonomy of children

Under the three possible dosage regimens under consideration, babies and young children would be the recipients of the varicella vaccine. Children under 16 years of age cannot legally consent to medical interventions and so parents must sign consent forms on their behalf. It is commonly accepted that children have a right to be protected from preventable harm, which implies a right to preventive medicine, and it is a parent's and a State's responsibility to take reasonable steps to ensure access.[202] Vaccination is provided to asymptomatic individuals to prevent the onset of illness and, as a result, its benefits may not be visible to the individuals who receive the vaccine. The herd effect that results from adequate vaccination coverage is often misunderstood as having a social, but not also an individual, benefit. As such, vaccination may be viewed as an intrusion on individual autonomy because in situations where vaccination is not mandated, individuals, particularly parents, may feel under pressure to comply with vaccination recommendations. While high rates of childhood vaccination coverage indicate that vaccination continues to be a widely accepted public health intervention, some individuals perceive it to be unnecessary.

The elements of valid informed consent are capacity, understanding of information disclosed, and voluntary agreement. As the proposed immunisation programme involves children who are too young to have the capacity to provide consent themselves, parents are requested to give consent on their behalf. It is important to ensure that children and adolescents, whose autonomy is developing, but not yet fully developed, have an appropriate role in the process of deciding whether or not to get vaccinated. However, given the proposed age at vaccination for varicella, it would not be appropriate to consider using a shared decision-making approach, although it is possible that children will grow up and disagree with the decisions that their parents have made on their behalf. Clear and comprehensible information is crucial to obtaining informed consent from parents for vaccination of their children. Informed consent materials must provide sufficient information in a form, manner and language that is comprehensible to parents; for example, in plain English. Additional resources may be required for translation and for review by adult literacy services, such as the National Adult Literacy Agency (NALA). Informed consent is underpinned by the provision of sufficient information. Sufficient time must also be afforded to parents and guardians to enable them to reflect on the choices available to them before making their decision.

In the event that the policy decision is not to extend the childhood immunisation programme to include varicella vaccination, there may be consequences for existing immunisation programmes if that decision is not adequately explained and publicised. In the absence of clear information then it may be speculated, for example, that the policy decision was on the basis of vaccine safety concerns, even though no major safety concerns were identified with the varicella vaccine (chapter 5). Such an outcome could undermine informed consent and, by extension, uptake of the existing childhood immunisation programme. Clear communication in relation to policy decisions on varicella vaccination may minimise the risk of misperceptions amongst the public and help support resilience in the existing programme.

Child assent and dissent should also be considered if the vaccine is administered to school-age children. Assent refers to the agreement of a child who is not legally able to give informed consent.[215] In their 2022 paper on consent for vaccination in children, Wilkinson and McBride suggest that the child should ideally be provided with age-appropriate information or explanation.[215] Dissent occurs when a child shows behavioural or verbal evidence of not wanting vaccination. Wilkinson and McBride also advise that for non-urgent interventions in older children, restraint is an option of last resort, and in some cases it may be in the child's best interest not to proceed.

Currently, consent to vaccinate a child is required from one parent or guardian only.[216] Consideration should be given as to what would happen in the case of parents with opposing views on whether to vaccinate their child against varicella.

### 9.3.2 Autonomy of healthcare workers

Healthcare professionals have a significant role to play as advocates for immunisation.[217, 218] The Guidelines for Vaccinations in General Practice in Ireland state that the GP should avail of every opportunity to promote vaccination.[185] Healthcare professionals are responsible for direct communication of health information to their patients, and their perception of vaccination programs can therefore influence the attainment of the national immunisation programme objectives.[219] Some healthcare workers may regard varicella as not severe enough to vaccinate against and therefore view the vaccine as unnecessary; other reasons for not supporting immunisation may include not believing the vaccine is effective and concerns regarding side effects of the vaccine.[218] In Ireland, GPs are incentivised for infants to complete their full vaccination schedule; where a GP has achieved the 95% uptake level for children under the age of two a bonus of €60.63 will be paid in respect of each child. This incentivisation may lead doctors to encourage vaccination, regardless of a personal moral opinion.

## 9.4 Respect for people

Varicella is a very common childhood illness and therefore, if introduced, a varicella vaccination programme will benefit the vast majority of children who receive the vaccine. As outlined in section 9.2.5.2, several countries have decided not to adopt a universal varicella vaccination programme, instead focusing on targeted at-risk groups. These decisions were influenced by the results of mathematical prediction models incorporating the exogenous boosting hypothesis, which predicted an increase in incidence of herpes zoster following the introduction of a varicella vaccination programme. Varicella vaccination programme decisions which are made with a strong emphasis on the exogenous boosting hypothesis are in danger of violating human dignity values as children may be seen as a means to achieving others' ends.[220] Where such decisions are made, children are purposefully not vaccinated, and therefore likely to contract varicella, to allow the circulating virus to 'boost' the immunity of adults who are most likely to develop herpes zoster.[220]

Certain religious or cultural groups may have a moral objection to immunisation, including varicella immunisation.[221] Religious, social and philosophical reasons follow medical reasons as the main reasons for vaccine exemption in countries with a mandated vaccination programme.[222] Vaccine avoidance on these grounds could affect vaccine uptake rates, however, it is unclear that varicella vaccination will give rise to a level of vaccine avoidance over and above what might be observed for the

other vaccines currently included in the childhood immunisation programme in Ireland.

It is important to respect people's privacy during the vaccination process. However, this can be particularly difficult in the school setting, where children would likely be able to tell if another child has or has not been vaccinated. Discrimination could occur on these grounds if a two-dose regimen, where the second dose is administered at four or five years of age, is recommended. Appropriate General Data Protection Regulation (GDPR) practices should be adhered to in all vaccination settings.

## 9.5 Justice and equity

Currently, the varicella vaccine is available in Ireland to those willing to pay privately for it. However, not all parents can afford the vaccine and not all parents are aware that it exists. The addition of varicella vaccination to the childhood immunisation schedule would ensure that the vaccine is available, free at the point of care, to all of those eligible to receive it.

Complications of varicella occur more frequently in immunocompromised people and infants less than 12 months of age. For these persons, varicella can be an extremely serious disease.[195, 223] Although varicella vaccination is contraindicated in both of these vulnerable groups, they may benefit from herd immunity, as described in section 9.2.5.1.

The three dosage regimens under consideration would involve vaccination in both the GP and school settings, with each having different access issues. Currently, all children under six years of age living in Ireland are entitled to a GP visit card which provides GP visits free at the point of care.[168] However, given previously highlighted GP capacity concerns, it would be important that the HSE continues to work with GPs and parents to ensure that those who consent to vaccination receive it, and that any barriers to access for disadvantaged groups are identified and minimised.

Members of the Irish Travelling community are less likely to access health services, including immunisation. Therefore, methods to increase uptake in this vulnerable group could be considered where necessary,[224, 225] such as the involvement of community healthcare workers from that community to provide peer-to-peer education and encouragement on health-related matters.[226]

Children who are home-schooled may be vaccinated at school or at a HSE clinic.[191] This is relevant for one of the two-dose regimens under consideration, where the second dose is administered at four or five years of age.

In Sligo, Leitrim and Donegal, children aged four to five years currently receive the 4 in 1 (diphtheria, polio, tetanus and whooping cough [pertussis]) booster vaccine and second dose of the MMR vaccine from their GP instead of at school. Similarly, it is expected that if a two-dose regimen was introduced, with the second dose administered at four or five years of age, that children in these counties would receive the second dose from their GP.[186] This may increase the burden on GPs in those counties.

### 9.5.1 Impact of the technology on the distribution of health care resources

The technology in question is a childhood varicella vaccination programme which will require in the region of 60,000 children to be vaccinated each year. For the one-dose regimen, it is assumed that the vaccine would be administered at the same 12 month GP appointment that occurs under the current immunisation schedule. Depending on how a two-dose regimen would be implemented, it may create a further 50,000 (assuming high uptake) GP visits per annum or alternatively it could leverage off the existing schools-based programme for children aged five years. This is markedly higher than the number of visits generated through varicella infection alone (chapter 3). However, over the longer-term, it would be anticipated that varicella vaccination would lead to a decrease in herpes zoster infections, which also create demand for GP care. As such, it may be considered that varicella vaccination would, in the short-term, create a net increase in demand for GP services. 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 varicella cases would lead to a reduction in associated hospitalisation, currently estimated at an average of 226 admissions per annum (chapter 3). So while vaccination may lead to an initial increase in demand for healthcare resources, that demand would be focused on prevention and would, in turn, lead to a reduced need for treatment. Varicella vaccination would result in a shift in demand from a secondary to primary care setting. The other advantage is that unlike infection, vaccination can be scheduled to improve efficiency and make better use of healthcare resources.

The introduction of a varicella immunisation programme would have upfront costs in the form of vaccine acquisition. The vaccines must be paid for upfront, while the full benefits in terms of reduced healthcare utilisation for both varicella and herpes zoster infection would take longer to realise. Those healthcare resources could be used elsewhere in the system, potentially with more immediate benefits in terms of reduced ill-health and healthcare utilisation.

## 9.6 Legislation

Mandatory vaccination policies are effective at improving vaccine uptake rates, often raising uptake to greater than 95%.[227] However, mandatory programmes have been debated extensively, and a range of sources have argued both in favour[228] and against[229] this approach. There are legal and ethical consequences associated with mandated vaccines. The right to bodily integrity is enshrined in the Irish Constitution[230] and there may also be implications for government liability in circumstances where individuals experience adverse events following vaccination.[231] In April 2019, the Minister for Health in Ireland asked the Attorney General to seek legal advice as to the constitutionality of introducing schemes of mandatory vaccination. In a response to a parliamentary question in 2020, the Minister stated that the legal advice was being reviewed by the Department of Health.[232]

The issue of discrimination on the grounds of vaccination status should also be considered.[233, 234] In Australia, where many states have strict policies requiring children to be fully vaccinated to attend childcare and early education services,[235] and the federal government can withhold social welfare payment for non-vaccination, parents described experiences that pointed to systematic stigmatisation.[236] Legislation rendered these parents unable to provide their children with the same early educational opportunities as vaccinated children.[236]

## 9.7 Ethical consequences of the Health Technology Assessment

### 9.7.1 Choice of outcomes

The effectiveness of varicella vaccination was considered in terms of protection against varicella, including severe disease, and herpes zoster. From an economic modelling perspective, the impact of a varicella immunisation programme is summarised by translating disease states into changes in quality of life. Given the rarity of mortality associated with varicella, an assumption of the model was that an immunisation programme would not lead to lives saved. By summarising illness into a set of discrete health states, there is a risk that an economic model over-simplifies the experience of ill-health. However, in the case of varicella, for most people the experience of infection is short-lived with no longer-term effects. 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.

### 9.7.2 Timing of the assessment

The evidence identified in chapters 4 and 5 on the effectiveness and safety of varicella vaccination was collected at a specific point in time and the conclusions could change over time, although this is unlikely given the abundance of evidence.

A varicella vaccination programme, if introduced, would begin with a particular cohort of infants of a particular age. Those not aged within that cohort, and therefore not eligible for vaccination, could be seen to be disadvantaged. At present, there is no plan for a mop-up programme, where those who were not previously eligible for the vaccine and have yet to receive it or develop the underlying disease would be targeted.

### 9.7.3 Evidence availability

Routine varicella vaccination was introduced in the USA in 1995. Therefore, there are over 25 years of data available for the efficacy and safety of the monovalent vaccine from the USA alone.[(203)] The quadrivalent MMRV vaccine was approved in the USA in 2005, and so there is also considerable evidence available on effectiveness and safety. Overviews of reviews, synthesising multiple systematic reviews incorporating studies from several countries, were conducted for the clinical efficacy (chapter 4) and safety (chapter 5) chapters because of the abundance of data.

### 9.7.4 Data sources and economic model assumptions

A number of the parameters in the economic model were subject to substantial uncertainty. Indeed, the values of some of the parameters were not known and had to be estimated through calibration. Some parameter values were based on reported estimates used in previously published cost-effectiveness analyses, but usage does not necessarily imply accuracy.

The approach to modelling in the HTA was deterministic due to the nature of the model type and computational overheads. As such, the ability to explore uncertainty has been limited. There is a theoretical risk that the findings of the HTA could be misleading because we have not been able to fully test parameter uncertainty. However, univariate sensitivity analyses, scenario analyses and a truncated probabilistic sensitivity analysis suggest that the findings are robust, particularly in relation to the one-dose strategy.

## 9.8 Discussion

This chapter considered the ethical issues that might arise with the expansion of the childhood immunisation schedule to include varicella vaccination.

The evidence of the effectiveness and safety of varicella vaccination identified in chapters 4 and 5 shows that the vaccine is both safe and effective in preventing varicella, particularly serious disease. A two-dose regimen is required for more complete prevention of varicella of any severity. A one-dose schedule has been included as a scenario in the economic model (chapter 7). Given the difference in efficacy between one-and two-doses, particularly with regard to breakthrough varicella, it is possible that a one-dose regimen may shift varicella infection to older age groups in some settings. This potentially creates a risk because varicella can be more severe for older children and adults.(198)

Speculation about the impact of varicella immunisation on the incidence of herpes zoster has been rife since the introduction of the varicella vaccine. Primary infection with the VZV results in varicella, while reactivation of the virus results in herpes zoster. The exogenous boosting hypothesis proposes that re-exposure to circulating VZV over a person's lifespan inhibits reactivation of the virus, and consequently, a person may be less likely to develop herpes zoster. However, long-term data (over 25 years) from the USA has failed to show the increased incidence of herpes zoster that was predicted based on this hypothesis.(203) In the UK, JCVI are revisiting the mathematical modelling of varicella vaccination based on this long-term data.(208)

The primary ethical concerns regarding varicella vaccination centre on the potential impacts on the current childhood immunisation schedule. The current national childhood immunisation programme targets diseases with serious symptoms and outcomes, including death.(210) While varicella can result in complications requiring hospitalisation, and death, these events are extremely rare (chapter 3). Among the general public, chickenpox may be seen as a rite of passage for young children, where they typically develop mild symptoms and acquire lifelong immunity. If varicella is generally viewed as a mild disease, adding varicella vaccination to the childhood schedule may have implications for the existing national immunisation programme. It could lead to a perception that the vaccine schedule is unimportant, thereby undermining the existing programme.

Based on the total number of births in Ireland in 2021, the estimated eligible population for varicella vaccination would be approximately 58,500 children per annum.(2) The healthcare budget is finite and adding varicella vaccination to the childhood immunisation schedule would require reallocation of or provision of additional resources. This could potentially impact the provision of other health technologies within the healthcare system. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity cost (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. Ethical issues that may inform such decisions include

issues of justice and equity with respect to a fair distribution of benefits and burdens.

Finally, many of the ethical issues discussed, for example, privacy and informed consent, are not unique to varicella vaccination and also apply to other vaccines in the national childhood immunisation schedule.

# 10 Discussion

## 10.1 Introduction

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 an expansion of the childhood immunisation schedule in Ireland to include varicella vaccination.

## 10.2 Findings of the Health Technology Assessment

Varicella-zoster virus (VZV) is associated with two distinct clinical syndromes, varicella, commonly known as chickenpox, which arises from primary infection with VZV and herpes zoster (HZ), commonly known as shingles, which results from reactivation of latent infection. A varicella vaccine was first developed in the 1970s with the vaccine serving as a primary prevention tool to prevent varicella and its sequelae. As part of this assessment, the different approved vaccines and potential vaccination schedules were outlined. As of March 2023, there were four varicella vaccines licensed in Europe, two of which are monovalent and two are quadrivalent (combined measles, mumps, rubella and varicella [MMRV]). All four vaccines are recommended to be used in a two-dose regimen by the manufacturers. Universal varicella vaccination (that is, vaccination of all children) is currently recommended and funded by the national health system in nine EU/EEA countries.[25] While all nine countries use a two-dose schedule, there is variability in terms of the type (monovalent or quadrivalent) of vaccine used and the timing of doses.

Currently, the annual number of cases of varicella in Ireland is approximately 55,000, with an estimated 59% of all cases occurring by the age of five years and 85% by the age of 10 years.[1, 45, 144] While the course of varicella disease is typically mild, serious complications and death can occur. For most cases of varicella, treatment is limited to supportive care, although antiviral medication may be considered in some cases. Between 2005 and 2016, there were an average of 226 hospital admissions per annum in Ireland associated with varicella, accounting for an average of 1,130 acute hospital and 161 ICU bed days per annum.[57] Infants (less than three years old) and young children (less than 10 years old) comprised the majority of admissions, at 47% and 76%, respectively. As the majority of varicella cases are in children, there may be significant costs for parents and caregivers in terms of the productivity loss associated with absence from paid work while providing care to sick children.

Once an individual recovers from varicella, VZV becomes latent in the person's nervous system and may reactivate resulting in herpes zoster (shingles). While

reactivation typically occurs several decades later, it can occur in childhood. Morbidity associated with herpes zoster increases with age and the most common complication, post herpetic neuralgia, can have a significant effect on quality of life.

Given the availability of numerous systematic reviews of the clinical effectiveness of varicella vaccination, an overview of reviews approach was adopted to assess the evidence of clinical effectiveness. There was clear and consistent evidence that vaccination is very effective at reducing varicella and its complications. The evidence suggests that two-dose strategies are more efficacious/effective than one-dose strategies in preventing varicella of any severity, but that one- and two-dose strategies have similar high efficacy/effectiveness in preventing moderate or severe varicella. Additionally, although evidence was limited with respect to two-dose strategies, there appears to be greater waning of immunity following one-dose than two-dose schedules.

A separate overview of reviews was used to assess the evidence of the safety of varicella vaccination. Overall, the evidence suggests that both monovalent and quadrivalent varicella vaccination are safe. While mild local and systemic reactions, such as fever and rash, are relatively common, serious adverse events are rare. The evidence also indicates that febrile seizures are possible adverse effects of both the monovalent varicella vaccine and the quadrivalent MMRV vaccine. The limited evidence on the co-administration of the varicella vaccine with other vaccines suggests that co-administration does not compromise the safety of the vaccines. The potential harms associated with varicella vaccination must be considered in light of the clinical benefits associated with reduced rates of incidence of varicella disease.

As part of this assessment, a cost-utility analysis of varicella vaccination in Ireland was undertaken. Three alternative vaccination strategies were analysed: one-dose (administered at 12 months), two-dose short interval (administered at 12 months and 15 months), and two-dose long interval (administered at 12 months and five years). From the payer perspective, a one-dose strategy was the least costly of all three vaccination strategies. Compared with no vaccination, the incremental cost-effectiveness ratio (ICER) for a one-dose strategy was estimated at €8,712 per quality-adjusted life year (QALY) gained. The two-dose long interval strategy was the next least costly option and compared with one-dose vaccination, the ICER was estimated at €45,090 per QALY gained. The two-dose short interval strategy was the most costly and most effective strategy and compared with the one-dose strategy, the ICER was estimated at €44,106/QALY gained. While the one dose strategy was cost-effective at a willingness-to-pay (WTP) threshold of €20,000/QALY gained, it was uncertain if the two-dose strategies would be cost-effective at a WTP threshold of €45,000/QALY gained. The budget impact over five years was estimated at €13.1 million, €28.1 million and €16.1 million for the one-dose, two-dose short interval,

and two-dose long interval strategies, respectively. The lower budget impact for the two-dose long interval strategy reflects the fact that only one birth cohort will complete the two-dose schedule within the five year time horizon of the BIA. The findings of this cost-utility analysis are not inconsistent with findings from recent economic evaluations of varicella vaccination conducted for a number of other countries as reported in chapter six. These economic evaluations adopted similar modelling approaches and while parameter data may have differed to those used in the present study, overall the findings were largely consistent. While our finding that the cost-effectiveness of the two-dose strategies relative to the one-dose strategy was close to the efficiency frontier at €45,000/QALY gained, all studies reviewed in chapter six compared two-dose vaccination with no vaccination only, with strategies largely cost-effective from both the payer and societal perspectives.

From an organisational perspective, the one-dose and two-dose long interval strategies capitalise on existing vaccination visits (in both GP practices and schools) as part of the current childhood immunisation programme. The two-dose short interval strategy creates a new GP visit to obtain the second dose at 15 months. The creation of an additional GP-based vaccination visit could create a challenge for the primary care system and also generate an additional burden on parents or guardians.

From an ethical perspective, given that varicella vaccination will be offered to children, their parents or guardians will be required to provide consent for vaccination. There may be a perception that chickenpox infection is inevitable and the majority of cases do not experience any serious outcomes, and hence vaccination is unnecessary. Therefore, if varicella vaccination is to be added to the childhood immunisation programme, an associated information campaign will be important to allay any concerns regarding the safety or efficacy of the vaccine and enable informed consent, and also to encourage high uptake. Also from an ethical perspective, while most cases of varicella occur by the age of ten years, introduction of a vaccination programme may shift infection into older age groups where there is a higher risk of severe disease.

## 10.3 Interpretation of the evidence

A HTA is founded on the synthesis of available evidence to address a specific policy question. The interpretation of that evidence is heavily influenced by the quality and quantity of information available, and the extent to which it is directly relevant and applicable to the policy question.

### 10.3.1 Burden of disease

Varicella infection is very common in Ireland, with most people infected at some point during their lifetime. Few people experience complications during infection and many cases do not result in a consultation with a doctor. As most consultations that do occur take place in a primary care setting, there are very limited centralised data available for analysis. The data available at a primary care level is based on a network of sentinel general practices, rather than full population coverage. While the sentinel practice data are nationally representative, they do not describe disease treatment or outcomes. Similarly, the data available on herpes zoster infection are based on consultation rates at a primary care level, although these data are likely to be representative given the expectation that most cases of herpes zoster would result in a GP consultation.

The other source of data available on varicella and herpes zoster in Ireland is the Hospital Inpatient Enquiry (HIPE) system, which records inpatient and day-case activity in Irish public acute hospitals. 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.

### 10.3.2 Clinical effectiveness

The varicella vaccine is a well-established technology, with studies assessing the efficacy and effectiveness of varicella vaccines published over the last 40 years. Both one- and two-dose strategies have been studied with a range of ages at vaccination, intervals between doses, and in specific settings or population subgroups. The data on effectiveness used in this assessment were collected using an overview of reviews approach, where the focus was on systematic reviews rather than the primary studies themselves. This approach has the benefit of leveraging off existing reviews rather than re-extracting and analysing the data. However, there are potential limitations. If the underlying reviews are of poor quality, then their interpretation of the evidence may be at risk of bias and a misleading representation of the evidence base. Eighteen of the 20 included systematic reviews were considered to be of 'critically low' quality using the AMSTAR 2 tool. It should be noted that the reviews were published over a long time span during which methodology for systematic reviews has developed and been increasingly formalised. The continued development and application of reporting guidelines also mean that more recent reviews tend to have higher quality ratings.

A key consideration in the assessment of the evidence of clinical effectiveness is the consistency of the findings across reviews. There was variability in the estimate of effectiveness of one-dose strategies, but less so for two-dose strategies. Another

important feature is waning immunity, but there was limited evidence of this available, particularly for two-dose strategies. Childhood vaccinations are often intended to give longer-term protection, and hence long-term follow-up is required to determine whether effectiveness is sustained. Gathering such long-term data can be costly and challenging in the context of a large trial, and such data are often then collected using observational studies, the findings of which may be at risk of confounding.

Another feature of interpreting clinical effectiveness data is the extent to which those data are applicable to the population of interest. Issues can arise, for example, if there is geographic variation in the disease of interest or its treatment. Another potential issue is if we are considering a general population when the available studies have focused on specific subgroups, such as people who are immunocompromised. The available data in this case related to a general population and the experience of varicella infection and the disease course was equivalent across studies, so there were no specific concerns about the applicability of the included populations. However, the population-level effectiveness of vaccination is generally closely linked to coverage, and not all studies clearly reported coverage, complicating interpretation of the evidence.

Although not reported in the systematic reviews included in the overview of reviews of the clinical effectiveness of varicella vaccination (chapter 4), long-term data (over 25 years) from the US, and more recently from Canada and Israel, document reduced rates of varicella-related invasive Group A streptococcal infections since universal routine varicella vaccination was adopted.[62, 237, 238]

### 10.3.3 Exogenous boosting

Herpes zoster infection results from reactivation of the varicella virus, potentially decades after initial varicella infection. The basis for the theory of exogenous boosting is that sub-clinical reactivation of the varicella virus provides a boost to immunity helping to prevent reactivation of the latent virus and the development of herpes zoster. The subclinical reactivation occurs due to exposure to infectious individuals with varicella. Under this hypothesis, if vaccination against varicella is introduced, the possible benefit from exogenous boosting would diminish and may result in increased incidence of herpes zoster among those susceptible to herpes zoster.

Consideration of the exogenous boosting hypothesis has been influential in decisions to not introduce varicella vaccination in other countries, such as the UK and Norway.[206, 207] However, long-term follow up data from the US, which has the longest running childhood varicella vaccination programme, have shown that the predicted increased incidence of herpes zoster among adults has not materialised.

While herpes zoster is more common in adults, the US data also show a pattern of decline in the incidence of herpes zoster in children which provides expectation that overall rates of herpes zoster will decline as vaccinated children age.[203]

The potential impact of exogenous boosting was explored in the economic evaluation presented in this report. If exogenous boosting is assumed to have an effect, then vaccination becomes less cost-effective. While a one-dose strategy would still be considered cost-effective at a willingness-to-pay (WTP) threshold of €20,000/QALY gained, two-dose strategies would not be cost-effective at a WTP of €45,000/QALY gained from a payer perspective. There is substantial uncertainty associated with the theory of exogenous boosting, giving rise to challenges in interpreting model results that incorporate it. Inclusion of exogenous boosting in the model requires assumptions about the strength and duration of effect that are unsupported by clear evidence. For this reason, it was only considered in a scenario analysis and not incorporated into the base case model.

### 10.3.4 Economic analysis

A significant component of the assessment was the economic modelling, used to estimate the cost effectiveness and budget impact of three potential varicella vaccination strategies. The model was developed specifically for this assessment and, in line with international practice that was reviewed as part of this assessment, a dynamic transmission model approach was used. Economic models attempt to model disease and treatment pathways in a manner that approximates the typical experience of individuals. To make it feasible to develop a model, a range of structural assumptions are generally made. These assumptions may result in the exclusion of relevant risks and outcomes, such as the risk of reinfection or the risk of mortality directly attributable to varicella infection. However, such assumptions reduce the complexity of the model and may reduce the reliance on parameter estimates that are supported by weak or limited evidence. The model was developed specifically for this assessment and, in line with international practice that was reviewed as part of this assessment, a dynamic transmission model approach was used. Consistent with national guidelines, the economic assessment was conducted from the publicly funded healthcare system in the base case analysis.[139] Given the potential for significant impact on productivity, due to absence from paid work to care for those with varicella, the societal perspective is also particularly relevant when conducting an economic assessment for varicella vaccination. In line with recommended good practice guidelines for the economic analysis of vaccination programmes, a societal perspective was therefore also adopted and reported.[137]

A potentially important structural assumption for this model was the use of a closed cohort population. The only addition to the population was an annual birth cohort. With the exception of age groups, the population in the model was also considered

homogeneous. These two assumptions have implications for how the model reflects what would happen if varicella vaccination was introduced. In the actual population, there is constant inward and outward migration, leading to constant mixing. Unvaccinated individuals can benefit from herd immunity while they remain in the population, but lose that benefit if they migrate to an unvaccinated population setting. Similarly an unvaccinated child that moves to a vaccinated population gains the benefit of herd immunity. The assumption of the homogeneous population ignores the fact that people live in communities that mix socially to a greater or lesser extent with other communities. The impact of vaccination in an open heterogeneous population may not be precisely estimated with a simulated closed homogeneous population. However, it should be noted that the main characteristics of varicella are well known and understood, and this model approach has been shown to be accurate.

In addition to structural assumptions, an economic model is reliant on a range of parameters that are combined to estimate the epidemiological and economic effects of vaccination. In this model, there were a wide range of parameters that were derived from numerous sources. Examples of parameters include: vaccine effectiveness, coverage, treatment costs, the probability that someone will require hospitalisation, and the impact on health-related quality of life of having varicella infection. While the data underpinning each parameter are assessed for plausibility, quality, and applicability, some were based on limited evidence. As is often the case, data on utilities for different health states came from a variety of sources and populations, creating challenges in determining whether they were directly comparable. The contact matrix that dictated interactions and the spread of disease was derived from UK data from 2006. The rate of reactivation from varicella to herpes zoster was estimated by calibrating the model against the observed incidence of herpes zoster.

Uncertainty in parameter data is typically addressed through a comprehensive probabilistic sensitivity analysis whereby all parameters are allowed to vary according to specified probability distributions. Those probability distributions are set to reflect uncertainty in the underlying data. By allowing all parameters to vary simultaneously, it is possible to explore decision uncertainty more thoroughly. In this assessment, the economic model involved an epidemiological model – the disease transmission model – that was associated with a substantial computational burden. While the model allowed for a more accurate estimate of the impact of vaccination on the spread of disease, it gave less scope for exploring uncertainty. However, extensive univariate sensitivity and scenario analyses were used to highlight the circumstances in which the results of the cost effectiveness of varicella vaccination may change. These analyses, along with a truncated probabilistic sensitivity analysis, demonstrated that the economic model findings were robust.

The difference in cost effectiveness between the short and long interval two-dose strategies was sensitive to the cost of administering the vaccine. The estimated cost in the GP practice setting was based on the fee paid for a number of existing childhood vaccinations.[178] There were no data available on the cost of administering the vaccine to five year olds as part of the schools-based vaccination programme. In line with standard economic modelling practice, a conservative approach should be adopted where data are lacking. Therefore, it was conservatively assumed that the cost in schools was the same as that in the GP practice setting. As the schools-based vaccination would potentially include four vaccines administered in a single visit, it is likely that the associated efficiencies would mean the cost of administering the varicella vaccine would be lower than was estimated. If the cost of administering is lower, then the two-dose long interval schedule would be more cost effective than estimated and would be associated with a lower budget impact.

### 10.3.5 Organisational issues

The effectiveness of a vaccination programme is linked to coverage and uptake. The WHO suggests that the target coverage for varicella vaccination should be at least 80% to prevent a shift in varicella infection to older age groups in some settings.[5] The coverage rates for vaccinations in the childhood immunisation programme in Ireland have historically been high.[151, 152] The addition of varicella vaccination to the programme could have an impact on existing coverage rates if parents either perceive it as unnecessary, due to the perception of varicella being a mild disease, or that it creates vaccine fatigue by creating more vaccine visits. In terms of a perception that it is not a necessary vaccination, the varicella vaccine is currently available privately and is being availed of. While there is evidence of a degree of demand and acceptability, in the absence of reliable coverage figures it is not possible to determine how widespread its use is.

In relation to the impact on uptake, two of the three modelled strategies do not involve the creation of a new vaccine visit. The two-dose short interval strategy would create a new vaccination visit that may impact uptake and overall coverage rates. It would potentially place a burden on parents or guardians and may require them to take additional time off work to bring their child to the GP. Additionally, increasing the number of GP visits required for childhood immunisation would generate an increased demand for primary care services. It could 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. While the one-dose and two-dose long interval strategies would leverage off the existing childhood immunisation programme schedule, adding an additional vaccine to the schedule would also impact on workload for GP practices and the schools immunisation teams.

### 10.3.6 Ethical and social considerations

The evidence of the effectiveness and safety of varicella vaccination indicates that the vaccine is both safe and effective in preventing varicella, particularly serious disease. While a two-dose regimen is required for more complete prevention of varicella of any severity, the difference in effectiveness between one-and two-doses, particularly with regard to breakthrough varicella, may shift the age distribution of varicella infection in unvaccinated individuals. This potentially creates a risk because varicella can be more severe for older children and adults.[198]

The primary ethical concerns regarding varicella vaccination centre on the potential impacts on the current childhood immunisation schedule. The current national childhood immunisation programme targets disease with serious symptoms and outcomes including death.[210] While varicella can result in complications and death, these events are extremely rare (chapter 3). Among the general public, chickenpox may be seen as an inevitable infection for young children, where they typically develop mild symptoms and acquire lifelong immunity. If varicella is generally viewed as a mild disease, adding varicella vaccination to the childhood schedule may have implications for the existing national immunisation programme where it could lead to a perception that the vaccine schedule is unimportant, thereby undermining the existing programme.

Additionally, consideration should be given as to whether a two-dose long-interval strategy specifically could create issues with uptake either if provided as a quadrivalent (MMRV) vaccine or, logistically, if a second injection was required (for example, MMR and a separate monovalent varicella injection). If there was a specific issue with uptake of the varicella vaccine, then that could by extension lead to reduced uptake of MMR if the combined MMRV vaccine was offered. However, in the absence of any evidence, it could also be argued that if a varicella vaccine had high acceptability, it may increase the uptake of the MMR vaccine.

The healthcare budget is finite and the addition of varicella vaccination to the childhood immunisation schedule would require funding estimated at between €13 million and €29 million annually, over the first five years of the programme. This funding requirement could potentially impact the provision of other health technologies within the healthcare system and therefore decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity cost of new investments are considered. Ethical issues of justice and equity with respect to a fair distribution of benefits and burdens may inform such decisions.

## 10.4 Conclusions

Varicella vaccination is highly effective and safe in preventing varicella, including severe disease. Based on the results of this assessment, which examined three potential vaccination strategies, a universal childhood varicella vaccination programme in Ireland would be an efficient use of resources. From the payer perspective, a one-dose strategy would be considered highly cost effective relative to no vaccination. From a societal perspective, a universal childhood varicella vaccination programme would be cost saving, with a two-dose short interval strategy being the most effective and least costly. Provision of a universal childhood varicella vaccination programme would be associated with ongoing annual programme costs, but would also result in costs averted due to a reduction in severe cases of varicella requiring hospitalisation. Implementation of a varicella vaccination programme would give rise to organisational implications that would differ depending on the vaccination strategy. A two-dose short interval strategy would likely have the greatest impact from an organisational perspective as it will require an additional GP visit at 15 months. Varicella vaccination would reduce the burden of varicella and herpes zoster on the healthcare system both in the short- and long-term owing to reductions in primary care consultations and hospitalisations for severe disease and complications. Additionally, from a societal perspective, varicella vaccination would reduce the significant productivity losses that arise for parents and caregivers when children with varicella, of any severity, require care. A final decision with regard to the choice between a one- and two-dose strategy possibly lies within the stated objective of such a programme and whether that would be to eliminate varicella or reduce hospitalisations and complications associated with the disease.

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# Appendices

## Appendix A4.1 Search strategies and grey literature search

| **Database Name** | Embase (Elsevier) | |
|---|---|---|
| **Date search run** | 2 February 2022 | |
| **#** | **Search string** | **Number of results** |
| #1 | chickenpox:ab,ti OR 'chicken pox':ab,ti OR varicella:ab,ti OR 'varicella-zoster virus':ab,ti | 21,855 |
| #2 | 'chickenpox'/exp | 13,311 |
| #3 | #1 OR #2 | 25,964 |
| #4 | vaccin* OR immuni* OR inocula*:ab,ti | 1,277,298 |
| #5 | varilrix OR varivax OR 'priorix tetra' OR proquad OR mmrv:ab,ti | 1,091 |
| #6 | 'vaccination'/exp OR 'immunization'/exp OR 'chickenpox vaccine'/exp OR 'chickenpox measles mumps rubella vaccine'/exp | 338,787 |
| #7 | #4 OR #5 OR #6 | 1,285,095 |
| #8 | (systematic NEAR/2 (review* OR overview*)):ab,ti | 296,650 |
| #9 | (literature NEAR/3 (review* OR overview*)):ab,ti | 410,442 |
| #10 | 'meta analys*':ab,ti OR 'meta analyz*':ab,ti | 279,930 |
| #11 | 'systematic review'/exp OR 'meta analysis'/exp | 441,459 |
| #12 | #8 OR #9 OR #10 OR #11 | 886,109 |
| #13 | #3 AND #7 AND #12 | 393 |

| **Database Name** | Medline Complete (EBSCO) | |
|---|---|---|
| **Date search run** | 2 February 2022 | |
| **#** | **Search string** | **Number of results** |
| S1 | AB ( Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus" ) OR TI ( Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus" ) | 16,938 |
| S2 | (MH "Chickenpox") | 7,678 |
| S3 | S1 OR S2 | 18,110 |
| S4 | AB ( vaccin* OR immuni* OR inocula* ) OR TI ( vaccin* OR immuni* OR inocula* ) | 713,757 |
| S5 | (MH "Vaccination+") OR (MH "Immunization+") | 192,239 |
| S6 | (MH "Chickenpox Vaccine+") | 3,086 |
| S7 | AB ( varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV ) OR TI ( varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV ) | 300 |
| S8 | S4 OR S5 OR S6 OR S7 | 769,302 |
| S9 | MH "Systematic Review" OR MH "Meta Analysis" OR PT "Meta-Analysis" 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 N2 (review* OR overview*) | 674,058 |
| S10 | S3 AND S8 AND S9 | 201 |

| **Database Name** | The Cochrane Library | |
|---|---|---|
| **Date search run** | 2 February 2022 | |
| **#** | **Search string** | **Number of results** |
| #1 | (Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus"):ti,ab,kw (Word variations will be searched) | 959 |
| #2 | MeSH descriptor: [Chickenpox] explode all trees | 132 |
| #3 | #1 OR #2 | 959 |
| #4 | (vaccin* OR immuni* OR inocula*):ti,ab,kw (Word variations will be searched) | 36,681 |
| #5 | (varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV):ti,ab,kw (Word variations will be searched) | 170 |
| #6 | MeSH descriptor: [Immunization] explode all trees | 5,226 |
| #7 | MeSH descriptor: [Chickenpox Vaccine] explode all trees | 206 |
| #8 | MeSH descriptor: [Vaccination] explode all trees | 2,752 |
| #9 | #4 OR #5 OR #6 OR #7 OR #8 | 36,798 |
| #10 | #3 AND #9 in Cochrane Reviews, Cochrane Protocols | 6 |

| **Database Name** | Google Scholar |
|---|---|
| **Date search run** | 2 February 2022 |
| **Search string** | **Number of results** |
| (intext:varicella OR intitle:chickenpox) (intext:vaccine OR intext:vaccination OR intext:immunise OR intext:immunisation OR intext:immunize OR intext:immunization OR intext:inoculate OR intext:inoculation)<br><br>Searched first five pages (100 results) and selected the option: 'sort by relevance' and used the limiter: Any type 'Review'. | 100 |

| **Database Name** | TRIP database |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| (title:varicella OR title:chickenpox) (vaccin* OR inocula* OR immuni*)<br><br>Search limited to results filtered with the label:"systematic reviews" | 42 |

| **Database Name** | International HTA database |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| ("Chickenpox"[mh]) OR (varicella OR chickenpox)[Keywords] | 3 |

| **Database Name** | Domain specific and google non-domain specific searches (see list of domains in table below) |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| "(intext:varicella OR intext:chickenpox OR intext:'chicken pox' OR intext:'chicken-pox') (intext:vaccine OR intext:vaccination OR intext:immunise OR intext:immunisation OR intext:immunize OR intext:immunization OR intext:inoculate OR intext:inoculation) (intext:'systematic review' OR intext:meta-analysis OR intext:meta-analyses)"<br><br>Search limited to 1,000 hits per website and filetype 'pdf'. | 1,000 |

| **Database Name** | TRIP database |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |

| | |
|---|---|
| (title:varicella OR title:chickenpox) (vaccin* OR inocula* OR immuni*)<br><br>Search limited to results filtered with the label:"systematic reviews" | 42 |

| **Database Name** | SYSVAC registry |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| Keyword search for "varicella" and "chickenpox" and combined results | 18 |

| **Database Name** | Prospero | |
|---|---|---|
| **Date search run** | 7 February 2022 | |
| **#** | **Search string** | **Number of results** |
| Multiple keyword searches (see #1 - #3) and a search for the MeSH term Chickenpox vaccine (#4). Results were scanned for relevant results. | | 10 |
| #1 | Varicella OR chickenpox | |
| #2 | Varicella vaccine* | |
| #3 | Chickenpox vaccine* | |
| #4 | MeSH DESCRIPTOR Chickenpox Vaccine EXPLODE ALL TREES | |

## Website domains for Heath Technology Assessment (HTA) agencies and Ministries of Health

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Norway | The National system for introduction of new methods in Specialist Health Care | nyemetoder.no |
| Norway | Norwegian Directorate of Health | helsedirektoratet.no |
| Norway | Norwegian Institute of Public Health (NIPHNO) | fhi.no |
| Norway | Norwegian Medicines Agency (NOMA) | legemiddelverket.no |
| Norway | Norwegian Centre for E-health Research | ehealthresearch.no |
| Norway | Ministry of Health and Care Services | regjeringen.no |
| Ireland | Health Information and Quality Authority (HIQA) | hiqa.ie |
| Ireland | National Centre for Pharmacoeconomics (NCPE) | ncpe.ie |
| Ireland | Department of Health | gov.ie |
| Switzerland | Federal Office of Public Health | bag.admin.ch |
| Switzerland | Swiss Network for HTA | snhta.ch |
| Switzerland | Federal Office of Public Health | bag.admin.ch |
| Hong Kong, China (SAR) | Department of Health | dh.gov.hk |
| Iceland | Ministry of Health | government.is |
| Germany | Federal Joint Committee (G-BA) | g-ba.de |
| Germany | Institute for Medical Documentation and Information (DIMDI) | dimdi.de |
| Germany | Institute for Quality and Efficiency in Health Care (IQWIG) | iqwig.de |
| Germany | Federal Ministry of Health | bundesgesundheitsministerium.de |
| Sweden | The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | sbu.se |
| Sweden | Medical Products Agency (Läkemedelsverket) | lakemedelsverket.se |
| Sweden | Dental and Pharmaceutical Benefits Agency (TLV) | tlv.se |
| Sweden | Ministry of Health and Social Affairs | government.se |
| Sweden | Public Health Agency (Folkhälsomyndigheten) | government.se |
| Australia | Pharmaceutical Benefits Advisory Committee | pbs.gov.au |
| Australia | Medical Services Advisory Committee | msac.gov.au |
| Australia | Department of Health | health.gov.au |
| Australia | Adelaide Health Technology Assessment, Univeristy of Adelaide | health.adelaide.edu.au |
| Australia | Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) | surgeons.org |
| Australia | Medical Services Advisory Committee | msac.gov.au |
| Australia | Pharmaceutical Benefits Scheme (PBS) | pbs.gov.au |
| Australia | Department of Health | health.gov.au |

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Netherlands | National Health Care Institute/ Zorginstituut | zorginstituutnederland.nl |
| Netherlands | Erasmus University Rotterdam | eur.nl |
| Netherlands | Utrecht University | uu.nl |
| Netherlands | Radboud University Medical Centre | radboudumc.nl |
| Netherlands | Organisation for Health Research and Development (ZonMw) | zonmw.nl |
| Netherlands | Ministry of Health, Welfare and Sport | government.nl |
| Denmark | Danish Health and Medicines Authority | sst.dk |
| Denmark | Social & Health Services and Labour Market Corporate Quality (DEFACTUM) | defactum.net |
| Denmark | Ministry of Health (Sundhedsministeriet) | sum.dk |
| Finland | National Institute for Health and Welfare | thl.fi |
| Finland | Finnish Coordinating Center for Health Technology Assessment | fincchta.fi |
| Finland | Finnish Medicines Agency (FIMEA) | fimea.fi |
| Finland | Ministry of Health and Social Affairs | stm.fi |
| Singapore | Performance & Technology Assessment Division, Ministry of Health | moh.gov.sg |
| Singapore | Ministry of Health | moh.gov.sg |
| Singapore | Agency for Care Effectiveness | ace-hta.gov.sg |
| United Kingdom | National Institute for Health Research | nihr.ac.uk |
| United Kingdom | National Institute for Health Research Innovation Observatory | io.nihr.ac.uk |
| United Kingdom | National Institute for Health and Care Excellence | nice.org.uk |
| United Kingdom | All Wales Therapeutics and Toxicology Centre | awttc.org |
| United Kingdom | Healthcare Improvement Scotland | healthcareimprovementscotland.org |
| United Kingdom | Health Technology Wales | healthtechnology.wales |
| United Kingdom | Department of Health & Social Care England | gov.uk |
| United Kingdom | Department of Health Northern Ireland | health-ni.gov.uk |
| United Kingdom | Health & Social Care Scotland | gov.scot |
| United Kingdom | Public Health Wales | phw.nhs.wales |
| Belgium | Belgian Health Care Knowledge Centre (KCE) | kce.gov.be |
| Belgium | Scientific Institute for Public Health | sciensano.be |
| Belgium | Institut national d'assurance maladie-invalidité (INAMI) | inami.fgov.be |
| Belgium | Federal Public Service Health, Food Chain Safety and Environment | health.belgium.be |
| New Zealand | National Health Committee | health.govt.nz |
| New Zealand | PHARMAC | pharmac.gov.nz |
| New Zealand | Ministry of Health | health.govt.nz |
| Canada | Canadian Agency for Drugs and Technologies in Health (CADTH) | cadth.ca |
| Canada | Insititute of Health Economics | ihe.ca |

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Canada | National Insitute of Excellence in Health and Social Services (INESSS) | iness.qc.ca |
| Canada | Ontario Health Canada | ontariohealth.ca |
| Canada | Health Canada | canada.ca |
| United States | Agency for Healthcare Research and Quality (AHRQ) | ahrq.gov |
| United States | Blue Cross Blue Shield Association | bcbs.com |
| United States | Center for Medical Technology Policy | cmtpnet.org |
| United States | Institute for Clinical and Economic Review | icer.org |
| United States | Kaiser Permanente | kaiserpermanente.org |
| United States | Patient Centered Outcomes Research Institute (PCORI) | pcori.org |
| United States | US Department of Human and Health Services (HHS) | hhs.gov |
| Austria | National Public Health Institute/ Gesundheit Österreich GmbH | goeg.at |
| Austria | Federation of Social Insurances/ Dachverband der Sozialversicherungsträger | sozialversicherung.at |
| Austria | Austrian Institute for Health Technology Assessment (AIHTA) GmbH | aihta.at |
| Austria | University for Health Sciences, Medical Informatics and Technology Tirol (UMIT) | umit.at |
| Austria | Ministry of Social Affairs, Health, Care and Consumer Protection | sozialministerium.at |
| Israel | Ministry of Health | health.gov.il |
| Japan | Medical technology evaluation team | pmda.go.jp |
| Japan | Ministry of Health, Labour and Welfare | mhlw.go.jp |
| Liechtenstein | Ministry of Social Affairs and Culture | regierung.li |
| Slovenia | Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) | jazmp.si |
| Slovenia | Ministry of Health | mz.gov.si |
| Slovenia | National Institute of Public Health | nijz.si |
| Slovenia | Ministry of Health | mz.gov.si |
| Korea (Republic of) | National Evidence-based Healthcare Collaborating Agency (NECA) | neca.re.kr |
| Korea (Republic of) | Ministry of Health and Welfare | mohw.go.kr |
| Luxembourg | Ministry of Social Security | mss.gouvernement.lu |
| Luxembourg | Ministry of Health | msan.gouvernement.lu |
| Spain | Spanish Network of Agencies for Health Technology Assessment and Services of the National Health System | redets.sanidad.gob.es |
| Spain | Agency for Medicines and Medical Devices | aemps.gob.es |
| Spain | Health Technology Assessment Agency (AETS) Institute for Health “Carlos III” | isciii.es |
| Spain | Andalusian HTA Agency (AETSA) | aetsa.org |

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Spain | Agency for Health Quality and Assessment of Catalonia (AQuAS) | aquas.gencat.cat |
| Spain | Foundation of Professor Novoa Santos | hospitalcoruna.sergas.es |
| Spain | Galician Agency for HTA (AVALIA-T) | avalia-t.sergas.es |
| Spain | Health Knowledge Agency (ACIS) | acis.sergas.es |
| Spain | Basque Foundation for Health Innovation and Research (BIOEF) | bioef.org |
| Spain | Directorate General for Pharmacy and Health Care Products (DGFPS MSPSI) | sanidad.gob.es |
| Spain | Andalusian Public Foundation on Progress and Health (FPS) | juntadeandalucia.es |
| Spain | Canarian Health Research Foundation (FUNCANIS) | funcanis.org |
| Spain | Evaluation and Planning Unit – Directorate of the Canary Islands Health Service (SESCS) | sescs.es |
| Spain | Basque Office for Health Technology Assessment (OSTEBA) | euskadi.eus |
| Spain | Health Sciences Institute of Aragon | aragon.es |
| Spain | Ministry of Health | mscbs.gob.es |
| France | Higher Health Authority/ Haute Autorité de Santé (HAS) | has-sante.fr |
| France | Public Assistance - Paris Hospital | aphp.fr |
| France | Ministry of Solidarity and Health | solidarites-sante.gouv.fr |
| Czechia | State Institute for Drug Control (SUKL) | sukl.eu |
| Czechia | Ministry of Health | mzcr.cz |
| Czechia | Ministry of Health | mzcr.cz |
| Malta | Office of the Chief Medical Officer | ehealth.gov.mt |
| Malta | Ministry of Health | health.gov.mt |
| Malta | Directorate for Pharmaceutical Affairs | health.gov.mt |
| Estonia | Institute of Family Medicine and Public Health, University of Tartu | tervis.ut.ee |
| Estonia | Ministry of Social Affairs | sm.ee |
| Italy | National Agency for Regional Health Services (AGENAS) | agenas.gov.it |
| Italy | Italian Medicines Agency (AIFA) | aifa.gov.it |
| Italy | Integrated University Hospital Verona | ospedaleuniverona.it |
| Italy | Ministry of Health | salute.gov.it |
| Italy | Region Emilia Romana | regione.emilia-romagna.it |
| Italy | Catholic University of the Sacred Heart Rome | roma.unicatt.it |
| Italy | Technology Assessment Unit, Padua Hospital, Veneto Region | sanita.padova.it |
| Italy | Veneto Region | regione.veneto.it |
| Italy | Regional Health & Social Agency (ASSR), Emilia Romana | assr.regione.emilia-romagna.it |
| Italy | HTA Unit in A.Gemelli Teaching Hospital | policlinicogemelli.it |
| Italy | Ministry of Health | salute.gov.it |
| United Arab Emirates | Ministry of Health and Prevention | mohap.gov.ae |

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Greece | National and Kapodistrian University of Athens | phs.uoa.gr |
| Greece | National Evalution Center of Quality and Technology in S.A.- EKAPTY | ekapty.gr |
| Greece | National Organization for Medicines | eof.gr |
| Greece | National Organisation for Healthcare Provision | eopyy.gov.gr |
| Greece | Institute of Pharmaceutical Research and Technology | ifet.gr |
| Greece | Onassis Cardiac Surgery Centre | onasseio.gr |
| Greece | Ministry of Health and Welfare | gov.gr |
| Cyprus | Pharmaceutical Services Ministry of Health | moh.gov.cy |
| Cyprus | Ministry of Health | moh.gov.cy |
| Lithuania | State Health Care Accreditation Agency under the Ministry of Health | vaspvt.gov.lt |
| Lithuania | Institute of Hygiene | hi.lt |
| Lithuania | State Medicines Control Agency | vvkt.lt |
| Lithuania | Ministry of Health | sam.lrv.lt |
| Poland | Agency For Health Technology Assessment and Tariff Systems (AOTMiT) | aotm.gov.pl |
| Poland | Ministry of Health | gov.pl |
| Andorra | Ministry of Health | salud.ad |
| Latvia | State Agency of Medicines | zva.gov.lv |
| Latvia | National Health Service | vmnvd.gov.lv |
| Portugal | INFARMED - National Authority of Medicines and Health Products | infarmed.pt |
| Portugal | Central Administration of the Health System (ACSS) | acss.min-saude.pt |
| Slovakia | Ministry of Health | health.gov.sk |
| Slovakia | Faculty of Pharmacy, Comenius University Bratislava | fpharm.uniba.sk |
| Hungary | National Institute of Pharmacy and Nutrition | ogyei.gov.hu |
| Hungary | Health Services Management Training Center (Semmelweis University) | semmelweis.hu |
| Saudi Arabia | Ministry of Health | moh.gov.sa |
| Bahrain | Ministry of Health | moh.gob.bh |
| Chile | Ministry of Health | minisal.cl |
| Croatia | Agency for Quality and Accreditation in Health and Social Welfare | aaz.hr |
| Croatia | Ministry of Health | miz.hr |
| Croatia | Health Insurance Fund (CHIF) | hzzo.hr |
| Croatia | Institute of Public Health | hzjz.hr |
| Croatia | Ministry of Health | miz.hr |
| Qatar | Ministry of Public Health | moph.gov.qa |
| Argentina | Institute for Clinical Effectiveness and Health Policy (IECS) | iecs.org.ar |

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Argentina | Ministry of Health | argentina.gob.ar |
| Brunei Darussalam | Ministry of Health | moh.gov.bn |
| Montenegro | Institute for Medicines and Medical Devices | calims.me |
| Montenegro | Ministry of Health | gov.me |
| Romania | National Agency for Medicines and Medical Devices | anm.ro |
| Romania | National Institute of Public Health | insp.gov.ro |
| Romania | National School of Public Health, Management and Professional Development | snspms.ro |
| Romania | Babes-Bolayi University, Cluj School of Public Health | publichealth.ro |
| Romania | Ministry of Health | ms.ro |
| Palau | Ministry of Health | palauhelath.org |
| International | International Centre for Community-Driven Research | cc-dr.org |
| International | World Health Organization | who.int |
| International | European Centre for Disease Prevention and Control | ecdc.europa.eu |
| International | Centers for Disease Control and Prevention | cdc.gov |

# Appendix A4.2 Data Extraction Tables

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Al Kaabi<br><br>2020<br><br>10.1080/21645515.2019.1638726<br><br>Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br><br>Database inception to 1 February 2016 | Individuals ≥12 months of age with breakthrough or primary varicella in the Middle East (specifically Iran, Iraq, the State of Palestine, Saudi Arabia, Turkey, and the United Arab Emirates (UAE))<br><br>Studies varied greatly in terms of size, with samples ranging from 102 to 20,788 patients.<br><br>Turkey (n=7 studies);<br>Saudi Arabia (n=2);<br>Abu Dhabi, United Arab Emirates (UAE) (n=1) | **One-dose**<br>Turkey<br>(vaccine type NR) | Total: 10 observational studies<br>(study type not reported) | NR and unvaccinated | ≥5yrs in one study (Turkey).<br>Others: NR | Incidence of varicella<br><br>Varicella associated complications<br><br>Varicella associated hospitalisation<br><br>Long-term persistence of protection based on incidence of breakthrough varicella over time | **Incidence of varicella**<br>Children aged 2-15.5yrs<br>(per 100,000 patient yrs)<br>Vaccinated: 4,550<br>Unvaccinated: 12,020<br><br>**Incidence and risk of varicella**<br>Preschool children (n=124) in an outbreak)<br>Vaccinated (1-dose): 24% had varicella<br>Unvaccinated: 34% had varicella<br><br>Risk 3.5 times higher in children vaccinated ≥5yrs versus those vaccinated more recently.<br><br>**Complications with varicella**<br>Non-hospitalised children in an outbreak<br>Vaccinated: no complications<br>Unvaccinated: 20.3% secondary skin infections, 18.6% vomiting, 11.8% diarrhoea, 6.7% vertigo and 5% pneumonia.<br><br>**Hospitalisation with varicella**<br>Incidence in children aged 1-5yrs<br>(per 100,000 children per year)<br>Pre-UVV: 6.1 to 9.1<br>Post-UVV: 3.1 to 4.3<br><br>Children (% hospitalised)<br>Vaccinated: 0.20%<br>Unvaccinated: 0.60%<br><br>Mean age of hospitalised children<br>Pre-UVV: 48.6mths<br>Post-UVV: 52.8mths<br>(mean age of hospitalised children was older post-UVV, p<0.005) | Although data on the impact of varicella vaccination in the Middle East are limited, the data that are available indicate that UVV has the potential to substantially reduce the clinical burden of the disease. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **Hospitalisation and complications with varicella**<br>Children<br>The proportion of children hospitalised with varicella and neurological complications was not significantly lower post-UVV versus pre-UVV.<br><br>Studies have reported cases of hospitalisation due to complications of breakthrough varicella, mainly neurological complications, fever and dehydration, respiratory complications, secondary bacterial infections, and haematological complications, e.g., in a study of 36 children hospitalised with breakthrough varicella, one patient with haematological oncological malignancy died due to varicella-related complications such as secondary bacterial infections and sepsis.<br><br>The percentage of children with seizures (including febrile seizures) was significantly reduced post-UVV versus pre-UVV. | | |
| | | **Two-dose**<br>Abu Dhabi, UAE and Saudi Arabia (vaccine type NR) | | | | Incidence of varicella | **Incidence of varicella**<br>(per 100,000 population)<br>Abu Dhabi<br>Pre-UVV (2011): 486<br>Post-UVV (2013): 147 to 168<br><br>Saudi Arabia<br>Pre-UVV (1994): 739.8<br>Post-UVV (2011): 88.1<br><br>Saudi Arabia armed forces hospital<br>Pre-UVV (2007): 754<br>Post-UVV (2012): 227 | | |

Key: CI – confidence interval; NOS – Newcastle Ottawa Scale; NR – not reported; UAE – United Arab Emirates; UVV – universal varicella vaccination; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Arlant<br><br>2019<br><br>10.1186/s12889-019-6795-0<br><br>Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br><br>Database inception to 1 February 2016 | Persons of any age and race in Latin America and the Caribbean who had primary and/or breakthrough varicella infection or were undergoing serological testing for antibodies to varicella | **One-dose monovalent**<br>Costa Rica (from 2007)<br>Coverage: 76% in 2008; 95% in 2015.<br><br>Uruguay (One-dose from 1999. Two-dose from 2014 but no data on impact of two-dose)<br>Coverage: 90% shortly after UVV introduction and maintained until 2013. | Total: 4 observational studies<br>Study type: not clear<br><br>Costa Rica (n=1 study)<br><br>Uruguay (n=3 studies) | Not vaccinated | Up to 7yrs post UVV introduction in 1 study (Costa Rica)<br><br>Up to 14yrs post UVV introduction in 1 study (Uruguay)<br><br>Others: NR | Incidence of varicella<br><br>Ambulatory visits associated with varicella<br><br>Hospitalisation associated with varicella<br><br>Complications with varicella<br><br>Mortality associated with varicella | **Costa Rica**<br>**Incidence of varicella** (Costa Rica)<br>• 7yrs post-UVV introduction (2008-2015): 74% reduction in reported varicella cases in the total population to 67/100,000 population and a 79% reduction in reported cases for children <5yrs.<br><br>**Hospitalisation associated with varicella** (Costa Rica)<br>• 86% reduction in varicella hospitalisations reported (87% in children aged <5yrs) for the post-(2008–2014) versus pre- (2000–2007) UVV era.<br>• Hospitalisations for complicated varicella decreased by 98%:<br>o 53 hospitalisations due to varicella complications (pneumonia, meningitis, or encephalitis) in 2008 versus one in 2014.<br><br>**Mortality associated with varicella** (Costa Rica)<br>Pre-UVV (2000-2007): n=23 deaths<br>Post UVV (2008-2014): n=24 deaths<br>Therefore showing no evident difference. However no information was available on the vaccination status of the deceased patients. | While there remains a need for additional local data, current evidence in LAC, as described in this review, provides an impelling rationale for the wider implementation of vaccination in this region.<br><br>For countries that have already implemented UVV, the challenge is to maintain high rates of coverage and, where relevant, consider inclusion of a | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **Uruguay**<br>**Incidence of varicella** (Uruguay)<br>• 2009: 10yrs post-UVV, incidence was 20/100,000 population.<br>• 2013 (outbreak): Among 151 cases of varicella infection detected in educational centers of one department, 97% were in vaccinated children.<br><br>**Ambulatory visits associated with varicella** (Uruguay)<br>• 2005: 6yrs post-UVV, incidence of ambulatory visits by children recorded by private insurance companies reduced by 87% compared to pre-UVV.<br>• Visits reduced by 80, 97, 81 and 65% in the <1, 1-4, 5-9 and 10-14yrs age groups respectively.<br><br>**Hospitalisation associated with varicella** (Uruguay)<br>• 2005: Hospitalisation rates in children decreased by 81% compared with pre-vaccination years (1997–1999), including decreases of 63, 94, 73, and 62% for < 1-, 1-4-, 5-9-, and 10-14-yrs age groups, respectively.<br><br>**Complications with varicella** (Uruguay)<br>• 1997-2005 (n=294,831 patients): 7% of children with breakthrough varicella had complications, compared with 12% of unvaccinated children.<br>• 2013 (outbreak): Among 151 cases of varicella infection detected in educational centers of one department, 97% were in vaccinated children. There were no serious cases and frequency of complications was low (4%). | second dose to reduce breakthrough cases. | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | **One-dose monovalent or quadrivalent MMRV**<br>Brazil<br>(One-dose from 2013. Two-dose from 2018 but no data on impact of two-dose) | Total: 3 studies<br>Case-control (n=1)<br>Others: study type not clear | Not vaccinated | | Incidence of varicella<br><br>Incidence of breakthrough varicella<br><br>Vaccine effectiveness any severity and moderate/severe varicella | **Brazil**<br>**Incidence of varicella**<br>Florianapolis, Brazil (children aged <2yrs vaccinated)<br>• After initiation of one-dose vaccination in 2002, 75.5% reduction in incidence of varicella in 1-4yr olds, compared with rising incidence in rest of the state where vaccination was not implemented.<br><br>Sao Paulo, Brazil<br>• Incidence from 2002 to 2017 (annual cases) show a trend to increasing numbers of cases up to introduction of vaccination in 2013:<br>o Pre-UVV (2013): n=25,052<br>o Post-UVV (2017): n=2,822<br><br>**Vaccine effectiveness**<br>Sao Paulo, Brazil (case-control study of children vaccinated with one-dose at 15mths)<br>• VE in 15-35mth olds against any severity varicella: 86%<br>• VE in 15-35mth olds against moderate/severe varicella: 93%<br>• Breakthrough rate: 22% - possibly attributable to vaccine failure, as the cases had been vaccinated only 9 months before, on average; patients with breakthrough varicella had less severe disease than non-breakthrough cases. | | |
| | | **One-dose and two-dose monovalent**<br>Puerto Rico (one-dose from 1996 and two-dose from 2007) | Total: 1 study<br>Study type: not clear | Not vaccinated | Up to 17yrs post UVV introduction | Hospitalisation associated with varicella | **Puerto Rico**<br>**Morbidity associated with varicella**<br>• Substantial decrease following the introduction of vaccination from 11.6 cases/100,000 in 1998 to 2.8 cases/100,000 in 2015. | | |

Key: LAC – Latin America and the Caribbean; MMRV – measles, mumps, rubella, varicella; UVV – universal varicella vaccination; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Bayer<br><br>2007<br><br>10.1016/j.vaccine.2007.07.010<br><br>LMUinnovativ (Ludwig-Maximilians University) research priority Project MCHealth<br><br>1995 to 31 Dec 2006 | n=3157 children, median age 4mths-12yrs (excluding those vaccinated before 12mths of age and those with prior history of varicella)<br><br>Outbreaks setting in day care centres or elementary schools | **One-dose** | Total: 14 studies<br>Study type unknown | No vaccination | Unclear | Vaccine effectiveness (VE) for prevention of varicella‡<br><br>‡ Cases defined in this review as children developing an acute maculopapulo-vesicular rash in the outbreak period or microbiologically confirmed (i.e., by PCR testing for VZV DNA of lesion specimens). | **Pooled VE (95% CI) for prevention of varicella**<br>(model unclear)<br>• Overall (n=16 estimates): 72.5% (68.5 to 76%)<br>• Immunisation coverage of the respective population was unrelated to VE. | This meta-analysis confirms a limited effectiveness of 1-dose of varicella vaccine and points to waning immunity as an important causal factor. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | **Subgroup analysis** | | | | | | | | |
| | n=918 children, median age 6mths-12yrs | **One-dose** | Total: 4 studies<br>Study type unknown | No vaccination | Range: 6mths – 72mths | Long term persistence of protection from varicella | Calculations showed substantial decrease in VE over time since immunisation. | | |
| | NR | | Total: 2 studies<br>Study type unknown | | Unclear | Long term persistence of protection from varicella | No relationship between VE and time since immunisation (not specified how this was assessed). | | |
| | NR | | Total: 7 studies<br>Study type unknown | | Unclear | Long term persistence of protection from varicella | Increased relative risk for contracting varicella after prolonged periods since immunisation. | | |

Key: DNA – deoxyribonucleic acid; NR – not reported; PCR – polymerase chain reaction; VE - vaccine effectiveness; VZV – varicella zoster virus

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Benchimol<br><br>2021<br><br>10.1093/jcag/gwab015 and 10.1053/j.gastro.2020.12.079<br><br>Guideline was funded by by the Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes, and CANImmunize.<br><br>Lead author supported by a New Investigator Award from the Canadian Institutes of Health Research, Crohn's and Colitis Canada, and CAG. He was also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program.<br><br>1989 to 12 April 2019 | Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy with the associated systematic review based on the general population (see below)<br><br>(While this paper relates to the development of immunisation guidelines for persons with inflammatory bowel disease, a systematic search for systematic reviews and meta analyses assessing the efficacy, effectiveness and safety of vaccines in the general population was also conducted). | **One-dose**<br>(vaccine type not reported)<br><br>**Two-dose**<br>(vaccine type not reported) | Total: 2 studies<br>Systematic reviews (SR): n=2<br>(1 SR includes a further 2 SRs)<br><br>Effectiveness outcome:<br>4 SRs of 42 observational studies<br><br>Safety outcome:<br>7 RCTs and 5 observational studies | No vaccination | NR | Vaccine effectiveness (VE) against all varicella<br><br>VE against moderate/severe varicella<br><br>VE against all varicella | **Pooled VE (95% CI) in preventing varicella infection in healthy children**<br>• 1 SR reported VE of 81% (78 to 84%)<br><br>**Pooled VE (95% CI) in preventing moderate/ severe varicella infection in healthy children**<br>• VE 98% (97 to 99%)<br><br>**Pooled VE (95% CI) in preventing varicella infection in healthy children**<br>• 1 SR reported VE of 92% (88 to 95%) | Maintaining appropriate vaccination status in patients with IBD is critical to optimise patient outcomes. In general, live vaccines are recommended in patients not on immunosuppressive therapy, but not for those using immunosuppressive medications. | **Risk of bias**<br>Cochrane RoB for RCTs and ROBINS-I for non-randomised studies<br>Assessment for individual studies not provided.<br>Overall deemed 'not serious' for effectiveness studies relating to healthy children in the general population.<br><br>**Overall quality of evidence assessment**<br>Effectiveness<br>GRADE certainty of evidence (CoE) for effectiveness was anchored to the general population (healthy children), adapted from WHO Evidence Tables, and started as **HIGH**. When the evidence was applied to IBD patients not on immunosuppressive medications, the evidence was downgraded to **MODERATE** due to indirectness as observational studies suggested that varicella vaccines may be less |

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| | | | | | | | | | immunogenic in IBD patients. |

Key: CI – confidence interval; CoE – certainty of evidence; IBD – inflammatory bowel disease; RCT – randomised controlled trial; SR – systematic review; VE – vaccine effectiveness; VZV – varicella zoster virus;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Di Pietrantonj<br><br>2021<br><br>10.1002/14651858.CD004407.pub5<br><br>National Institute for Health Research (NIHR) via the NIHR Cochrane Incentive Award Scheme 2018 - 128383<br><br>Medline from 1966 and Embase from 1974 to 2 May 2019 | Healthy children aged up to 15yrs, or adults who received MMR or MMRV/ MMR+V vaccination between 0 and 15yrs of age.<br><br>RCTs only: Approximately 3,000 healthy children aged 11-22mths at vaccination with MMR or MMRV/MMR+V vaccine. | **One-dose monovalent**<br>Varivax (n=1)<br>Multiple (n=1) | Total: 2 studies<br>**Case control** (n=2) | No vaccination | NR | Vaccine effectiveness (VE) against varicella‡ – any severity<br><br>‡defined in this review as clinical and/or laboratory-confirmed | **Pooled VE (95% CI) against <u>any severity varicella</u>**<br>(random effects model) ¥<br>• Overall (n=2 estimates): 86% (78 to 92%, $I^2$=0%)<br><br>¥in this review quantitative synthesis is performed on adjusted estimates | Our review shows that MMRV and MMR+V vaccines are effective in preventing the infection of children by chickenpox with no evidence of an increased risk of autism or encephalitis and a small risk of febrile seizure.<br><br>More evidence is needed to assess whether the protective effect of MMRV could wane with time since immunisation. | **Risk of bias**<br>Risk of bias conducted for all primary studies. RCTs assessed using criteria adapted from the *Cochrane Handbook for Systematic Reviews of Interventions*<br><br>Case-control (prospective and retrospective) and cohort studies assessed using the appropriate Newcastle-Ottawa Scales.<br><br>Case-only ecological method studies, self-controlled case series and person time cohort studies assessed for *case selection, exposure, observation and exposure risk* |
| | | **One-dose monovalent**<br>(Varilrix)<br>(varicella vaccine administered with 2nd dose MMR) | Total: 3 studies<br>**RCT** (n=3) | 2-dose MMR vaccine<br>(no varicella vaccination) | Up to 5yrs;<br>5-10yrs;<br>Up to 10yrs | VE against varicella - any severity<br><br>Long-term persistence of protection against varicella - any severity | **Pooled VE (95% CI) against <u>any severity varicella</u>**<br>(random effects models)<br>• Overall (up to 10yrs) (n=3 estimates): 67% (64 to 70%, $I^2$=0%)<br>• 5yrs (n=1 estimate): 65% (57 to 72%)<br>• 5-10yrs (n=1 estimate): 67% (62 to 71%)<br>• 10yrs (n=1 estimate): 67% (62 to 71%) | | |
| | | | | | | Vaccine effectiveness (VE) against varicella – moderate/severe<br><br>Long-term persistence of protection against varicella – moderate/severe | **Pooled VE (95% CI) against <u>moderate/severe varicella</u>**<br>(fixed effects model)<br>• Overall (up to 10yrs (n=3 estimates): 90% (88 to 92%, $I^2$=0%)<br>• 5yrs (n=1 estimate): 91% (86 to 94%)<br>• 5-10yrs (n=1 estimate): 90% (87 to 93%)<br>• 10yrs (n=1 estimate): 90% (86 to 92%) | | |
| | | | Total: 1 study<br>**RCT** (n=1) | | 5-10yrs | Long-term persistence of protection against varicella – severe | **VE (95% CI) against <u>severe varicella</u>**<br>(fixed effects model)<br>• Overall (n=1 estimate): 95% (53 to 99%) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | **One-dose quadrivalent**<br>MMRV ProQuad (n=1)<br>MMRV Priorix-Tetra (n=3) | Total: 4 studies<br>**Cohort study** (n=4) | No vaccination | NR | Vaccine effectiveness (VE) against varicella - any severity | **Pooled VE (95% CI) against <u>any severity varicella</u>**<br>(random effects model)<br>• Overall (n=4 estimates): 75% (41 to 89%, $I^2$=98%)<br>• MMRV ProQuad (n=1 estimate): 94% (92 to 96%)<br>• MMRV Priorix-Tetra (n=3 estimates): 62% (61 to 63%) | | *period and comparability.*<br><br><u>Efficacy/ Effectiveness studies</u><br>8/14 (57%) varicella studies rated 'low', 4 (29%) rated 'unclear' and 2 rated 'high' (14%) risk of bias.<br><br>**Overall quality of evidence assessment**<br>GRADE Quality of Evidence assessment applied for **RCTs** examining VE against varicella of 2-dose MMRV and 1-dose MMR+V. Certainty of evidence rated as HIGH. |
| | | **Two-dose monovalent**<br>Varivax (n=1)<br>Multiple (n=1) | Total: 2 studies<br>**Case control** (n=2) | No vaccination | NR | VE against varicella – any severity | **Pooled VE (95% CI) against <u>any severity varicella</u>**<br>(random effects model)<br>• Overall (n=2 estimates): 95% (86 to 99%, $I^2$=0%) | | |
| | | **Two-dose quadrivalent**<br>MMRV Priorix-Tetra | Total: 2 studies<br>**Cohort study** (n=2) | No vaccination | NR | Vaccine effectiveness (VE) against varicella - any severity | **Pooled VE (95% CI) against <u>any severity varicella</u>**<br>(random effects model)<br>• Overall (n=2 estimates): 87% (86 to 87%, $I^2$=0%) | | |
| | | **Two-dose quadrivalent**<br>MMRV Priorix-Tetra | Total: 3 studies<br>**RCT** (n=3) | 2-dose MMR vaccine only (no varicella vaccine) | Up to 5yrs;<br>5-10yrs;<br>Up to 10yrs | Long-term persistence of protection against varicella - any severity | **VE (95% CI) against <u>any severity varicella</u>:**<br>(random effects model)<br>• 5yrs (n=1 estimate): 95% (92 to 97%)<br>• 5-10yrs (n=1 estimate): 95% (94 to 96%)<br>• 10yrs (n=1 estimate): 95% (94 to 96%) | | |
| | | | | | | Long-term persistence of protection against varicella – moderate/severe | **VE (95% CI) against <u>moderate/severe varicella</u>:**<br>(random effects model)<br>• 5yrs (n=1 estimate): 100% (98 to 100%)<br>• 5-10yrs (n=1 estimate): 99% (98 to 100%)<br>• 10yrs (n=1 estimate): 99% (98 to 100%). | | |
| | | **At least one-dose monovalent**<br>Varivax (n=1)<br>Not defined (n=1) | Total: 2 studies<br>**Case control** (n=2) | No vaccination | Unknown | VE against varicella – any severity | **Pooled VE (95% CI) against <u>any severity varicella</u>**<br>(random effects model)<br>• Overall (n=2 estimates): 88% (82 to 92%, $I^2$=0%) | | |
| | | **At least one-dose quadrivalent**<br>MMRV Priorix-Tetra | Total: 1 study<br>**Case control** (n=1) | | | VE against varicella - any severity | **VE (95% CI) against <u>any severity varicella</u>**<br>(random effects model)<br>• Overall (n=1 estimate): 86% (72 to 93%) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | VE against varicella – moderate/severe | **VE (95% CI) against <u>moderate/severe varicella</u>**<br>(random effects model)<br>• Overall (n=1 estimate): 93% (83 to 97%) | | |
| | | **At least one-dose quadrivalent**<br>MMRV | Total: 2 studies<br>**COEM study**<br>(n=2) | | | VE against varicella incidence (by age group) | **VE (95% CI) against <u>incidence of varicella</u>**<br>(random effects model)<br>• Overall (n=5 estimates): 76% (57 to 86%, $I^2$=100%)<br>• Age <1yr (n=1 estimate): 83% (76 to 88%)<br>• Age 1-4yrs (n=1 estimate): 92% (91 to 93%)<br>• Age 5-14yrs (n=1 estimate): 86% (84 to 88%)<br>• Age 0-14yrs (n=2 estimates): 35% (20 to 47%, $I^2$=98%) | | |
| | | | Total: 3 studies<br>**COEM study**<br>(n=3) | | | VE against hospitalisation with varicella | **Pooled VE (95% CI) against <u>hospitalisation</u>**<br>(random effects model)<br>• Overall (n=7 estimates): 57% (45 to 66%, $I^2$=60%)<br>• Age <1yr (n=2 estimates): 48% (26 to 63%, $I^2$=0%)<br>• Age 1-4yrs (n=2 estimates): 71% (15 to 90%, $I^2$=88%)<br>• Age 5-14yrs (n=2 estimates): 63% (21 to 81%, $I^2$=68%)<br>• Age 0-14yrs (n=1 estimate): 47% (36 to 56%) | | |

Key: CI – confidence interval; COEM – case only ecological method; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; NR – not reported; rr – rate ratio; RR – risk ratio; VE - vaccine effectiveness;

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|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Garrido<br><br>2012<br><br>10.32385/rpmgf.v28i2.10928<br><br>No funding received<br><br>January 2005 to November 2009 | Healthy children aged 1-12yrs at vaccination<br><br>Sample sizes varied across included studies (449 to 135,311) but were not reported for all studies | **One-dose** (vaccine type not reported) | Total: 11 studies<br>Systematic reviews (SRs) (n=3);<br>Meta-analysis (n=1);<br>Primary studies (n=7) | No vaccination or placebo | Various:<br><br>Up to 10yrs in one clinical trial<br><br>Up to 3yrs in one primary study<br><br>Up to 2yrs in one SR | Incidence of varicella<br><br>Vaccine effectiveness against varicella (any severity)<br><br>Vaccine effectiveness against varicella (moderate-severe disease)<br><br>Vaccine effectiveness against varicella (severe disease)<br><br>Long term persistence of protection based on incidence of breakthrough varicella (BV) over time | **Vaccine effectiveness**<br>• A SR analysing 41 (mostly observational) studies published in the USA concluded that:<br>o 1-dose has 80 to 85% effectiveness in preventing any severity chickenpox and >95% in the prevention of severe chickenpox.<br>o the American vaccine programme has reduced the incidence of chickenpox by 57 to 90%, with the biggest decline seen in children <10yrs old but with an increase in age in the peak of incidence (3-6yrs in 1995 to 9-11yrs in 2005).<br>o the occurrence of outbreaks, even in populations of school children with high vaccination coverage, indicates that 1-dose is insufficient to generate herd immunity and to prevent the transmission of wild virus between vaccines.<br>• A SR analysing 17 observational studies concluded that despite 1-dose providing excellent protection (VE 80 to 85% in preventing any severity varicella and 97 to 100% in preventing severe varicella), a higher VE is needed to interrupt transmission and prevent outbreaks. VE is less than that estimated (98% after 2yrs follow-up) in a RCT pre-introduction of the vaccine.<br>• In a SR analysing 1 SR (including 2 RCTs) and another RCT, there were no significant | Considering the available evidence, it can be concluded that the varicella vaccine is an effective intervention and safe in healthy children, not only because of the decrease in incidence but also in the associated morbidity and mortality. However, its implementation should be universal in order to allow a high coverage rate, and the possibility of two doses may be considered. In the future, further studies will be needed to assess the effectiveness and long-term impact of varicella vaccination. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>The Strength of Recommendation Taxonomy (SORT) scale from the American Family Physician Foundation was used.<br><br>3 of the 4 SRs/meta-analysis and 1 of the 7 primary studies were graded as Level 1 evidence (good quality patient orientated evidence). The remaining studies were not graded. |

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| | | | | | | | differences in incidence in the RCT, although the placebo group had a higher risk of moderate to severe disease (RR 8.0, 95% CI: 1.21 to 51.51). In the first RCT included in the SR, VE was 100% at 24mths post-vaccination while VE was 97% at 29mths post-vaccination in the 2nd RCT. Overall, authors reported decreased incidence at 2yrs post-vaccination, decreased severity of disease and concluded the vaccine had high global effectiveness.<br>• A meta-analysis based on 14 observational studies of outbreaks in primary schools, reported an overall VE of 72.5%, but varying considerably between studies (20 to 100%).<br>**Long term persistence of protection**<br>• A meta-analysis based on 14 observational studies of outbreaks in primary schools reported that 9 of the studies evaluated the decrease in immunity over time:<br>o 2 studies found no relationship between vaccination time and decreased immunity, but did not specify how they came to that conclusion.<br>o 7 studies verified, based on relative risk, that the longer the post-immunisation period, the greater the probability of BV occurring in previously vaccinated children. | | |
| | | **Two-dose** (vaccine type not reported) | | No vaccination or placebo | | Vaccine effectiveness against varicella | **Vaccine effectiveness**<br>• A SR reported 2-dose VE of 98.3% (95% CI: 97.3 to 99%) in an observational period of 10yrs. | | |

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| | | **Two-dose** (vaccine type not reported) | | One-dose (vaccine type not reported) | | Incremental vaccine effectiveness (2-dose versus 1-dose) | **Incremental vaccine effectiveness**<br>• A SR that compared 1 and 2 doses concluded that children receiving 2 doses had a 3.3 fold lower risk of breakthrough varicella and vaccine effectiveness (VE) increased significantly after 2 doses (VE 98.3% [95% CI, 97.3 to 99.0%]) versus 1-dose (VE 94.4% [95% CI, 92.9 to 95.7%]) (p<0.001). | | |
| | | **At least one dose** (vaccine type not reported) | | No vaccination | | Incidence of varicella<br><br>Rate of breakthrough varicella<br><br>Vaccine effectiveness against varicella (any severity)<br><br>Vaccine effectiveness against varicella (moderate/ severe)<br><br>Hospitalisation associated with varicella | **Vaccine effectiveness**<br>• An observational study in Sicily reported that incidence of varicella decreased from 95.7 to 9/1,000 children per year over a 3yr period following introduction of the vaccine. The reduction was seen in all age groups.<br>• An observational study in Brazil, comparing the pre- and post-vaccination periods, reported a 75.5% reduction in incidence of varicella in the 1-4yr old age group. In the other age groups there was no statistically significant reduction with VE of 37.75%.<br>• A retrospective cohort study in a school outbreak setting (n=1,134 children) reported a varicella breakthrough rate of 11.2% and an effectiveness rate of 81% (coverage 63%).<br>• A case-control study reported that VE of 88% for varicella of any severity and VE of 100% for moderate/severe disease in the first 3yrs after vaccination.<br><br>**Hospitalisation associated with varicella**<br>• An retrospective study in USA comparing pre- and post-UVV reported: | | |

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| | | | | | | | o the hospitalisation rate for varicella decreased from 15.7 to 5.5 cases/100,000<br>o the rate of admission to the ER fell from 178.2 to 61.2 cases/100,000. This may not only be due to the vaccine but also better access to primary care and earlier prescribing of acyclovir<br>o no significant difference in mean age of children hospitalised<br>o no significant difference in number of days hospitalised (4.3 vs 3.9 days in the pre- and post-vaccination period, p=0.50). | | |

Key: BV – breakthrough varicella; ER – emergency room; RCT – randomised controlled trial; SR – systematic review; USA – United States of America; UVV- universal varicella vaccination; VE – vaccine effectiveness;

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|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Goh<br><br>2019<br><br>10.1080/14760584.2019.1594781<br><br>Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br><br>Database inception to 1 February 2016 | Adults, infants, and children of any race and gender in the Asia Pacific region without evidence of immunity to VZV.<br><br>Taiwan (n=7 studies);<br>Australia (n=8);<br>South Korea (n=1) | **One-dose**<br>Taiwan<br>(from 2004)<br><br>Australia<br>(from 2005)<br>Coverage: 78.4% in 2007<br><br>South Korea<br>(from 2005)<br>Coverage: 97% in 2011<br><br>(vaccine type not reported) | Total: 16 studies<br>Study type: observational studies/ epidemiological datasets (breakdown not provided) | Pre-vaccination era | 10yrs for severe hospitalised varicella (Australia)<br><br>Others not reported | Incidence of varicella<br><br>Complications associated with varicella<br><br>Hospitalisation associated with varicella<br><br>Mortality associated with varicella | **Taiwan**<br>**Incidence of varicella** (Taiwan)<br>• Data from 3 studies indicate a 2.9- to 3.8-fold reduction from the post-vaccine era to the UVV era.<br><br>**Hospitalisation associated with varicella** (Taiwan)<br>• Data on hospitalisations were limited and varied.<br>• Admission rate with varicella ranged from 0.99/10,000 admissions in the post-vaccination era (children) to 68/10,000 in the pre-vaccination era (overall population).<br>• Admission rate due to varicella increased to 139/10,000 dermatological admissions in the post-vaccination era.<br>• 1 study reported a significant reduction in the hospitalisation rate following approval of the vaccine: 68/10,000 admissions in the pre-vaccine era to 34/10,000 admissions in the post-vaccine era (p <0.001).<br><br>**Complications associated with varicella** (Taiwan)<br>• 1 study reported that the proportion of patients with neurological complications significantly reduced (p=0.01) in the post-vaccine era versus pre-vaccine era.<br>• Frequency of pneumonitis increased (p=0.05), in the post-vaccine era versus pre-vaccine era.<br>**Mortality associated with varicella** (Taiwan)<br>• A similar case-fatality rate in patients hospitalised for varicella complications was observed during the post-vaccine era (1998–2004) compared with the pre-vaccine era (1988–89) (1.3% vs. 2.2%, respectively. | Universal varicella vaccination programs have uniformly shown a reduction in varicella infection in those vaccinated. Hospitalisation rates were significantly decreased after access to varicella vaccine. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | • In another study, a lower fatality rate of 0.05% of hospitalised varicella cases was reported during the post-vaccine era, 2000-03.<br>**Australia**<br>**Incidence of varicella** (Australia)<br>• Increase in incidence post-UVV (2005) from 17.8/100,000 population in 2006 to 19.6/100,000 population in 2008.<br>• Grey data from the Australian Department of Health also suggest an increasing trend in varicella incidence.<br>• However, the seemingly low number of cases reported highlights potential under reporting, reducing confidence in the data.<br><br>**Hospitalisation associated with varicella** (Australia)<br>• The hospitalisation rate per 100,000 population ranged from 4.0 (1995–99) to 11 (1998–99) in the pre-vaccine era, 4.2 (2006–10) in the post-vaccine era, and 2.9 (2006–10) to 3.1 (2006–07) in the UVV era.<br>• Stepwise reductions observed in the annual incidence of varicella hospitalisation per 100,000 population as follows:<br>o pre-vaccination era: 6.1<br>o post-vaccination era: 5.3<br>o UVV era: 2.9<br>• 10-year follow up study reported that after introduction of a one-dose vaccine, vaccinated children were less likely to have severe hospitalised varicella defined as >7 days of stay and/or ICU management (9% vaccinated vs. 21%, unvaccinated).<br>• Highest hospitalisation rate observed in infants <1 year (57.1/100,000, 44.5/100,000, and 21.7/ 100,000 in the pre-vaccine, post-vaccine, and UVV eras, respectively).<br>• Access to vaccine did not seem to influence the duration of hospitalisation, which ranged from 3.3 to 7.4 days. | | |

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| | | | | | | | **South Korea**<br>**Incidence of varicella** (South Korea)<br>• Grey data suggest an increasing incidence of varicella post-UVV.<br>• The KCDC did not begin reporting varicella incidence until 2005. Between 2005 and 2009, the number of reported cases rose steadily from 1934 in 2005 to 25,197 in 2009, likely reflecting not so much changes in varicella incidence but the impact of implementation of the varicella notification system.<br>• 2010 was the first year that a decline was reported, followed by a rise in 2011, a decline in 2012, and steady rises after that.<br>• 16.7% increase in notified varicella cases between 2015 and 2016 (from 46,330 in 2015 to 54,060 in 2016). | | |

Key: ICU – intensive care unit; KCDC - Korean Centers for Disease Control and Prevention; UVV - universal varicella vaccination; VE - vaccine effectiveness; VZV - varicella-zoster virus

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|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search date | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Hong<br><br>2017<br><br>Article number: 1006-916X(2017) 03-0331-06<br>http://www.cqvip.com/qk/90851a/201703/672760216.html<br><br>Funding source not provided<br><br>Period before 2016 | n=46,455 children and students in varicella outbreak clusters in China (involving >20 cases)<br><br>n=4,613 children and students for case-control studies<br><br>n=41,842 children and students for cohort studies | **One-dose** (type not specified) | Total: 18 studies<br>**Case-control** (n=10)<br>**Retrospective cohort** (n=8) | No vaccination | <3yrs to 10yrs | Vaccine effectiveness for prevention of varicella‡<br><br>‡Clinically or laboratory diagnosed varicella used in this review | **Pooled VE against varicella (95% CI)**<br>(fixed effects model)<br>Overall (n=18 estimates):<br>VE 73% (71 to 76%, $I^2$=22%)<br><br>Case-control studies (n=10 estimates):<br>VE 70% (66 to 74%, $I^2$=22%)<br><br>Cohort studies (n=8 estimates):<br>VE 74% (70 to 77%, $I^2$=16%) | Varicella vaccination has good VE, and VE decreases with the passage of vaccination interval in cluster outbreaks. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | **Subgroup analysis** | | | | | | | | |
| | n=1,033 children aged 12mths-3yrs | **One-dose** (type not specified) | Total: 2 studies<br>**Retrospective cohort** (n=2) | No vaccination | <3yrs | Vaccine effectiveness for prevention of varicella | **Pooled VE against varicella (95% CI)**<br>(fixed effects model)<br>VE 98% (95 to 99%, $I^2$=38%) | | |
| | n=1,115 children aged 4-6yrs | | Total: 3 studies<br>**Retrospective cohort** (n=3) | | 3-5yrs | | **Pooled VE against varicella (95% CI)**<br>(fixed effects model)<br>VE 92% (87 to 95, $I^2$=58%) | | |
| | n=881 children aged 7-9yrs | | Total: 3 studies<br>**Retrospective cohort** (n=3) | | 6-8yrs | | **Pooled VE against varicella (95% CI)**<br>(fixed effects model)<br>VE 70% (45 to 83%, $I^2$=17%) | | |
| | N=464 children and students | | Total: 2 studies<br>**Retrospective cohort** (n=2) | | 9-10yrs | | **Pooled VE against varicella (95% CI)**<br>(fixed effects model)<br>VE 54% (-2.0 to 58%, $I^2$=0%) | | |

Key: CI – confidence interval; VE - vaccine effectiveness;

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| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Kaufmann<br><br>2020<br><br>10.1080/14760584.2020.1825947<br><br>GlaxoSmithKline Biologicals SA<br><br>1994 to NR (date of last search not reported) | Persons who received varicella vaccination as part of a paediatric varicella vaccination program in Germany or Italy | **Italy:**<br>**One-dose monovalent**<br>(regional implementation since 2003; regional recommendation until 2017)<br>Coverage: In 2012, one-dose coverage across 8 Italian regions reached 84 to 95% in 24mth olds (Sicily, Puglia, Basilicata, Calabria, Friuli Venezia Giulia, Sardinia, Tuscany, and Veneto). In 2015, one-dose coverage across the 8 regions was between 53 and 84% (at which time quadrivalent MMRV was also being administered). | Surveillance studies (n=8) | No vaccination | NR | Incidence of varicella | **Incidence of varicella**<br>• In a number of pilot regions, incidence decreased by 30-80% depending on coverage. In 2 regions (Sicily and Puglia), incidence decreased by ≥89%.<br>• A nationwide surveillance study also indicated that there was a significant decrease in incidence from 164 cases in 2006 to 101 cases per 100,000 in 2009 (p<0.01). | Substantial reductions in incidence of moderate/ severe varicella‡ and varicella-related hospitalisation occurred during the 1-dose era.<br><br>Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively.<br><br>Different benefit-risk evaluations of a quadrivalent (MMRV) vaccine used as a first dose led to different recommendations (MMRV versus MMR+V) in these countries.<br><br>‡Moderate and severe | The 'Cochrane grading system for bias' was used, although not clear what tool was used:*<br>• Low risk of bias (n=74)<br>• Unclear risk of bias (n=8)<br>• High risk of bias (n=41)<br>* Review included a total of 123 studies, not all of which were relevant for this overview of reviews.<br><br>The analysis focused primarily on publications with a low risk of bias and those that provided information collected in a consistent way both before and after the introduction of UVV in Italy and Germany.<br><br>**Overall quality of** |
| | | | Study type: NR (n=2)<br>Data sources: Surveillance/ hospital and regional database | No vaccination | Within 4yrs after UVV introduction | Hospitalisation associated with varicella | **Hospitalisation associated with varicella**<br>• 3 regions reported significant reductions in varicella-related hospitalisations as soon as 4 years after the introduction of UVV (p=0.0004 for Puglia and p<0.0001 for both Veneto and Sicily). The same study also showed that compared with non-UVV regions, varicella incidence and varicella-related hospitalisation rates declined more rapidly in UVV regions (p=0.0428 and 0.0427, respectively).<br>• 2 other regions (Tuscany and Puglia) reported decreases in varicella-related hospitalisation of 44% and 26% respectively, within 4yrs following introduction of UVV. | | |
| | | | Study type: NR (n=1)<br>Data source: Epidemiological/ hospital records | No vaccination | Within 4yrs after UVV introduction | Complications associated with varicella | **Complications associated with varicella**<br>• 1 region reported a decrease in complications from 57 cases in 2002 to 14 in 2007. | | |
| | | **Germany:**<br>**One-dose monovalent from 2004 and** | Surveillance studies (n=3)<br>Others (study type NR) (n=4) | No vaccination | Up to 10yrs post vaccination | Incidence of varicella<br><br>Vaccine effectiveness against varicella | **Incidence of varicella**<br>• 2 surveillance studies demonstrated that 1-dose UVV decreased incidence by approx. | | |

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| | | **quadrivalent MMRV from 2006** (national implementation since 2004)<br>Coverage: After the introduction of the 1-dose varicella UVV program, coverage rates generally increased year by year up to 65%. | | | | | 63–75% in children ≤4 years of age.<br>• At a regional level, significant decreases in varicella incidence were also reported in Munich, Bavaria.<br><br>**Vaccine effectiveness**<br>• VE 86.6% (95% CI: 85.2 to 87.9) based on a nationwide surveillance study of health insurance claims data in the period 2009-2014.<br>• VE 72% (95% CI: 59-81%, p< 0.001)) based on a surveillance study of outbreaks in day-care centres, with no difference by age, day-care centre, or gender.<br>• 1-dose was shown to be highly effective in 1–2-, ≤4-, and ≤16-year-olds. | varicella not defined. | **evidence assessment**<br>Not conducted |
| | | | Study type: NR (n=3)<br>Data source: Surveillance/ hospital discharge data | No vaccination | Up to 7yrs after UVV introduction | Hospitalisation associated with varicella | **Hospitalisation associated with varicella**<br>• 65% decrease in hospitalisations from 13.3 to 4.8 per 100,000 people over a 6yr period since UVV introduced.<br>• Decreases of a similar and significant magnitude were observed when data on hospitalisations from 2005 to 2012 were compared with data from the pre-UVV era (p<0.05). Reductions greatest in the <1 and 1-4yr age groups, at 61.3% and 62.6%, respectively.<br>• A single study on varicella-related hospitalisations between 2004 and 2010 demonstrated that a 2-fold increase in vaccine coverage was associated with a two-fold decrease in hospitalisations. | | |
| | | | Epidemiological study (n=1) | No vaccination | Within 5yrs after UVV introduction | Complications associated with varicella | **Complications associated with varicella**<br>• % of varicella-related complications decreased in all age groups from 0.4% in 2005/2006 (first season of UVV) | | |

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| | | | | | | | to 0.2% by 2008/2009 (fourth UVV season). | | |
| | | **Italy:**<br>**Two-dose monovalent, quadrivalent MMRV or both**<br>(regional implementation from 2005 and national implementation from 2017) | Study type: NR (n=3)<br>Data source: Epidemiological database/analyses | No vaccination | Various including up to 9yrs after UVV introduction | Incidence of varicella | **Incidence of varicella**<br>• Pooled data from all 8 regions that had implemented regional UVV programs since 2003 showed a substantial reduction of varicella cases by 2012.<br>• In 3 regions varicella incidence fell below 0.5 cases per 1000 person years by the fourth year after UVV commenced and in a fourth region by the sixth year after the introduction of UVV.<br>• In Sicily, varicella notifications decreased by >95% between 2003 and 2012. | | |
| | | | Study type: NR (n=3)<br>Data source: Epidemiological database/analyses | No vaccination | Various | Hospitalisation associated with varicella | **Hospitalisation associated with varicella**<br>• A study of nationwide hospital databases revealed a decrease in hospitalisation rates from 4.2 per 100,000 inhabitants in 2002 and 2004 to 1.9 per 100,000 in 2013 and 2014, coinciding with the introduction of regional UVV from 2003 to 2013.<br>• Pooled data from all 8 regions that had implemented regional UVV programs since 2003 showed a substantial reduction of varicella-related hospitalisations by 2012.<br>• In Sicily and Puglia, the incidence of varicella-related hospitalisations dropped to 0.8 and 1.1 per 100,000 person years by 2012 and 2009–2012, respectively. | | |
| | | **Germany:**<br>**Two-dose monovalent, quadrivalent or both**<br>(national implementation from 2009)<br>From 2011, MMR+V vaccinations were recommended for the | Surveillance studies (n=2)<br>Others (study type NR) (n=5)<br>Data sources: Surveillance/ sentinel data, hospital discharge data, health insurance claims, | No vaccination and NA | Within 5yrs after UVV introduction | Vaccine effectiveness (VE) (and coverage)<br><br>Incidence of varicella | **Vaccine effectiveness (VE)**<br>• 1 study reported 2-dose VE of 97.3% (95% CI: 85.2 to 87.9) based on a nationwide surveillance study of health insurance claims data in the period 2009-2014.<br>• 1 study showed that 2-dose effectiveness for all combinations of varicella and MMRV vaccines | | |

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| | | first dose instead of MMRV.<br>Coverage: By 2015, coverage for the 1st dose was 80-90% and < 4% who got the 1st dose weren't getting the 2nd dose. | paediatric practice data | | | | ranged between 94.3% (95% CI: 93.9–94.8) and 95.0% (95% CI: 94.3–95.5) suggesting that the type of vaccine administered and the order do not influence effectiveness.<br><br>**Incidence of varicella**<br>• The overall picture indicates 3- to 4-fold decreases in the incidence of varicella infection with the introduction of the 2-dose UVV program. However, UVV has not eradicated varicella infection, with coverage rates ranging from 70%–90% depending on the study, year, and region. | | |
| | | | Study type: Surveillance study (n=1)<br>Data Source: Surveillance/health insurance claims | Interval between dose 1 and dose 2 | NR | Vaccine effectiveness | **Vaccine effectiveness**<br>• Interval of 28 days to 3 years between vaccinations had no effect on VE. | | |
| | | | Study type: Epidemiological prospective matched case-control study (n=1) | Age at vaccination | NR | Vaccine effectiveness | **Vaccine effectiveness**<br>• Age at vaccination of <15 vs ≥15 months did not influence vaccine effectiveness. | | |
| | | | Study type: Sentinel network surveillance study (n=1) | 1-dose | Within 5yrs after 2-dose UVV introduction | Incidence of breakthrough varicella (BV) | **Incidence of BV**<br>• Of 111,456 varicella cases identified between 2005 & 2014, 4,357 were breakthrough cases. Of these, 80% of were in children who had received 1 dose of vaccine and 20% in those who had received 2 doses. | | |
| | | | Study type: NR (n=1)<br>Data Source: Surveillance/health records and patient questionnaires | 1-dose | NR | Incidence of breakthrough varicella | **Incidence of BV**<br>• 2 doses of vaccine were associated with a lower risk of breakthrough than a single dose. | | |
| | | | Study type: NR (n=1)<br>Data Source: National hospital discharge data | No vaccination | Within 3yrs after 2-dose UVV introduction | Hospitalisation associated with varicella | **Hospitalisation associated with varicella**<br>• Mean age-adjusted incidence of varicella-related hospitalisations decreased from 3.3 to 1.9 per | | |

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| | | | | | | | 100,000 person years after UVV introduction (2005–2012 period), with the highest declines observed in regions with the highest vaccination coverage. | | |
| | | **Italy:**<br>**At least one-dose monovalent, quadrivalent MMRV or both** | Surveillance study (n=1) | No vaccination | Within 3yrs after UVV introduction | Incidence of breakthrough varicella | **Incidence of BV**<br>• In 1 region, BV decreased from 40.5% of cases of varicella infection in the 2008 (2-dose UVV introduced 2009) birth cohort to 4.5% in the 2011 birth cohort. | | |

Key: BV - breakthrough varicella; MMRV - measles, mumps, rubella, varicella; MMR+V – measles, mumps, rubella + varicella (2 vaccines administered concomitantly); NA - not applicable; NR - not reported; UVV - universal varicella vaccination; VE - vaccine effectiveness;

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|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Marin et al.<br><br>2016<br><br>10.1542/peds.2015-3741<br><br>US CDC<br><br>1995 to 15 December 2014 | Immunocompetent children aged 12mths to 18yrs. (Outcomes predominantly calculated among preschool and elementary school-aged children).<br><br>Settings included child-care centres, schools, community clinical practices, hospitals, outpatient setting, and households in the following countries: United States (n=23 studies), China (n=4), Germany (n=3), Israel (n=3), Italy (n=2), Spain (n=2), Taiwan (n=2), Australia (n=1), Turkey (n=1), and Uruguay (n=1). | **One-dose monovalent**<br>Varivax (n=23 studies)<br>Varilrix (n=9)<br>Unspecified (n=6)<br>Multiple (n=6)<br>Baike (n=1)<br>Changsheng (n=1)<br>Keygen (n=1)<br>Okavax (n=1)<br>Shanghai (n=1)<br>*Some studies reported data on >1 named vaccine brand. | Total: 42 studies<br>Retrospective cohort (n=29)<br>Matched case-control (n=10)<br>Prospective cohort (n=1)<br>Time-series regression model (n=1)<br>Household contact study (n=1) | NR | Varied; <10yrs is likely median time since vaccination | Vaccine Effectiveness (VE) for prevention of:<br>• all varicella‡<br>• moderate/severe¥ varicella<br>• severe varicella<br>• varicella-related hospitalisation<br><br>‡ In measuring outcomes, 37/42 studies used clinically diagnosed varicella with details on illness obtained from parents; 5 studies used laboratory confirmed varicella.<br><br>¥In 18/30 studies, severity of disease was defined as mild, <50 lesions; moderate, 50-500 lesions; and severe, ≥500 lesions or a serious complication or hospitalisation; other studies used a different number of lesions to define severe disease: >250 lesions, >200 lesions, and >150 lesions, or assessed severity based on a disease-severity score modified from the clinical trials, a combination of criteria that included number of days with fever, number of | **Pooled VE (95% CI) for prevention of <u>all varicella</u>** (random effects model)<br>• Overall (n=58 estimates): 81% (78 to 84%, $I^2$=88%)<br>• Varivax (n=26 estimates): 82% (79 to 85%, $I^2$=62%)<br>• Varilrix (n=10 estimates): 77% (62 to 85%, $I^2$=92%)<br>• Other vaccines (n=5 estimates): 86% (78 to 91%, $I^2$=39%)<br>• Mixed/multiple (n=17 estimates): 81% (76 to 85%, $I^2$=85%)<br><br>**Pooled VE (95% CI) for prevention of combined <u>moderate and severe varicella</u>** (random effects model)<br>• Overall (n=34 estimates): 98% (97 to 99%, $I^2$=85%)<br>• Varivax (n=18 estimates): 98% (95 to 99%, $I^2$=86%)<br>• Varilrix (n=6 estimates): 98% (89 to 100%, $I^2$=79%)<br>• Other vaccines (n=1 estimate): 100% (91 to 100%, $I^2$=NR)<br>• Mixed/multiple (n=9 estimates): 99% (95 to 100%, $I^2$=86%)<br><br>No significant association between VE and vaccine type or study design.<br><br>**VE for prevention of <u>severe varicella</u>**<br>• 100% (n=24 estimates)<br>• 85% (n=1 estimate for prevention of varicella-related hospitalisations). | One dose of varicella vaccine was moderately effective in preventing all varicella and highly effective in preventing moderate/ severe varicella, with no differences by vaccine. The second dose adds improved protection against all varicella.<br><br>Assessment of vaccine effectiveness in recipients who are >10 to 20 years after vaccinations with both 1 and 2 doses is needed. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

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| | | | | | | lesions, number of days the patient needed rest and presence of complications, hospitalization only, or parental subjective assessment of severity. | | | |
| | | **One-dose quadrivalent**<br>Priorix-Tetra (n=1 study) | Total: 1 study<br>Retrospective cohort study (n=1) | NR | Unclear | VE for prevention of:<br>• all varicella<br>• severe varicella*<br>*not clear what type of varicella diagnosis and what definition for varicella severity applies. | **VE (95% CI) for prevention of <u>all varicella</u>**<br>• Priorix-Tetra (n=1 estimate): 55% (8 to 78%)<br><br>**VE for prevention of <u>severe varicella</u>**<br>• Priorix-Tetra (n=1 estimate): 100% | | |
| | | **Two-dose monovalent**<br>Breakdown of vaccine brands not provided (n= 8 studies) | Total: 8 studies<br>Cohort studies (n=4)<br>Case-control studies (n=4) | NR | Unclear (5 years reported in 1 study) | VE for prevention of:<br>• all varicella*<br>*not clear what type of varicella diagnosis applies. | **Pooled VE (95% CI) for prevention of <u>all varicella</u>**<br>(random effects model)<br>• Overall (n=8 estimates): 92% (88 to 95%, $I^2$=57%) | | |
| | | **Two-dose quadrivalent**<br>Priorix-Tetra (n=1 study) | Total: 1 study<br>Cohort study (n=1) | NR | Unclear | VE for prevention of:<br>• all varicella*<br>*not clear what type of varicella diagnosis applies. | **VE (95% CI) for prevention of <u>all varicella</u>**<br>• Priorix-Tetra (n=1 estimate): 91% (65 to 98%) | | |

Key: CI – confidence interval; MMRV – measles, mumps, rubella, varicella; NA – not applicable; NR - not reported; VE - vaccine effectiveness;

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| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Meszner<br><br>2019<br><br>10.1080/14760584.2019.1573145<br><br>Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA<br><br>Database inception to 1 February 2016 | Males or females of any age and race who had primary and/or breakthrough varicella or were undergoing serological testing for antibodies to varicella in Central and Eastern Europe (CEE) (defined as Albania, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Serbia, Slovakia, and Slovenia).<br><br>Latvia (n=1 study) | **One-dose quadrivalent MMRV**<br><br>Latvia<br>(One-dose from 2008. Two-dose from 2019 but no data on impact of two-dose) | Total: 1 study<br>Study type: not clear | NR | NR | Incidence of varicella<br><br>Hospitalisation associated with varicella | **Latvia**<br>**Incidence of varicella**<br>• Although specific data on the impact of vaccination in Latvia have not been published, the low incidence of varicella recorded in 2010 (second only to Cyprus) appears to confirm the effectiveness of vaccination.<br><br>**Hospitalisation associated with varicella**<br>• The EUVAC surveillance study described wide variations in hospitalisation rates across CEE. Highest hospitalisation rates were reported in Latvia, the only CEE country with mandatory universal vaccination; it is possible that stringent medical practices and prioritisation of varicella as a public health concern contribute to the hospitalisation rates in Latvia, although interpretation is complex. | Limited data availability precludes an analysis of changes in varicella incidence following the introduction of vaccination in CEE. Despite the dearth of data, the evidence from this region (similar to that from other areas of the world) suggests that introduction of varicella vaccination programs provides benefit from both patient and public health perspectives.<br><br>For countries that do not provide UVV, introduction of vaccination is predicted to provide substantial reductions in cases and rates of associated complications, with important economic benefits. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

Key: CEE – Central and Eastern Europe; EUVAC - European surveillance network for vaccine-preventable diseases; MMRV – measles, mumps, rubella, varicella;

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| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| New Zealand National Health Committee<br><br>2012<br><br>DOI: NR; Link: https://www.moh.govt.nz/notebook/nbbooks.nsf/0/1BA074BCCABF911ACC257F7F000A4101/$file/nhc-varicella-vaccine-assessment-report.pdf<br><br>Funding: Review conducted by an independent statutory authority<br><br>1 January 2009 to 16 September 2011 (HTA Agency & repositories); to 2 November 2011 (MEDLINE & Cochrane and 16 November 2011 (EMBASE) | Children aged 0-5yrs | **One-dose**<br>(vaccine type NR) | Total for overall VE: 17 studies including case control, cohort (outbreak) and house contact studies.<br><br>Germany: n=1 study<br>Analysis of sentinel dataset | No vaccination | NR | Vaccine effectiveness against varicella (any severity)<br><br>Vaccine effectiveness against varicella (moderate/severe) | **Vaccine effectiveness**<br>• VE against all varicella: 81%<br>• VE against moderate and severe varicella combined: 97%<br>• VE against severe varicella: 100%<br><br><u>Germany</u><br>• Evidence of a reduction in the number of varicella cases in 4 consecutive seasons following the introduction of the vaccination programme. The decrease was greatest in 0-4yr olds, but the trend was seen in all age groups. | Evidence suggests that all single-antigen vaccines currently available for varicella are clinically effective for most children aged 15 months and 4 years, alongside existing immunisations on the schedule. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | | Total: 5 studies<br>Study type NR<br><br>USA: n=3 studies; Australia: n=1 study; Germany: n=1 study (descriptive analysis of sentinel dataset) | No vaccination | Up to 16yrs after UVV implementation in the USA | Hospitalisation associated with varicella | **Hospitalisation associated with varicella**<br><u>USA</u><br>• Since the implementation of the 1-dose vaccination program in 1995, varicella related hospitalisation numbers and rates declined significantly.<br>• It has been argued that the impressive decline in varicella deaths can be directly attributed to the successful implementation of the 1-dose vaccination programme.<br><br><u>Australia</u><br>• Between 2000 and 2007 (1-dose vaccine publicly funded since 2005) varicella hospitalisation rates declined by 7% each year, predominantly in children <5yrs (12%) and a similar decline was observed in community data. | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Germany<br>• Descriptive analysis of sentinel data provided evidence of a reduction in the number of cases in four consecutive seasons following the introduction of the vaccination programme. The decrease was greatest in 0-4yr olds, but the trend was seen in all age groups.<br>• In the 3 years after the general recommendation of varicella vaccination the annual number of hospitalised varicella cases steadily declined from 1,751 in 2005 to 1,269 in 2007. The decline in number of hospitalised cases per 100,000 population was largest in the age group 1-4 yrs old (from >20 hospitalised varicella cases per 100,000 population in 1994-2004 to 10 in 2007) and in infants (from >30 hospitalised varicella cases in 1994-2004 to 21 in 2007). | | |
| | | **Two-dose** (vaccine type NR) | Total: 17 studies including case control, cohort (outbreak) and house contact studies | No vaccination | NR | Vaccine effectiveness against varicella (any severity) | **Vaccine effectiveness**<br>• VE against all varicella: 98% | | |

Key: MMRV – measles, mumps, rubella, varicella; MMR+V – measles, mumps, rubella vaccine and varicella vaccine administered concomitantly; NR – not reported; USA – United States of America; VE – vaccine effectiveness

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Pallas<br><br>2011<br><br>DOI: Not published<br><br>Funding: Systematic review commissioned by the ECDC and conducted by Pallas Health Research Consultancy, Rotterdam, the Netherlands. An ECDC report partially updated this systematic review with searches up until 8 June 2012, with one new study relevant for the current overview of reviews identified. For completion, the single relevant additional study is added here.<br><br>Pubmed:<br>1 September 1995 to 1 September 2010<br><br>Embase:<br>1995 to 2011 | Human subjects vaccinated with VZV vaccine | **At least one-dose monovalent or quadrivalent MMRV** (multiple brands) | Total: 7 studies<br>SR (n=3 ->15 unique studies including 9 RCTs and 6 observational studies);<br>RCT (n=1);<br>Other (n=3); | No vaccination or placebo | Up to 7yrs; 9mths | Vaccine effectiveness (VE) against varicella (any severity)<br><br>Vaccine effectiveness (VE) against varicella (moderate/severe) | **Vaccine effectiveness**<br>• Overall, varicella vaccination appears to be effective, with VE rates around ≥80%.<br>• VEs for preventing moderate/severe disease (measured in 4 studies) was between 97% and 100%.<br>• It seems that 2 doses of varicella vaccine are more effective than 1 dose in preventing varicella disease. | The effectiveness of monovalent varicella vaccines and quadrivalent MMRV vaccines seem to be supported sufficiently by a large amount of evidence. However, due to large heterogeneity between studies, it is often difficult to summarise the evidence. | **Risk of bias**<br>The methodological quality of the articles were, when possible, critically appraised using the Evidence Based Medicine CoCanCPG checklists, specific for each study design. However, no results were presented for included studies.<br><br>**Overall quality of evidence assessment**<br>No overall quality of evidence assessment undertaken. If available, the level of evidence of included studies was graded and reported in Evidence Tables using a grading system for evidence-based medicine developed by the Dutch Institute for Healthcare Improvement (CBO). |
| | | **At least one-dose monovalent or quadrivalent MMRV** (multiple brands) | Total: 9 studies<br>SR (n=3);<br>MA (n=1 ->15 unique studies;<br>Other (n=5); | No vaccination | NR | Vaccine effectiveness (VE) in outbreak settings (schools and child care centres) | **Vaccine effectiveness in outbreak settings**<br>• VE for varicella vaccination in outbreak settings ranged between 20% and 93%.<br>• VE for moderate/severe disease appears to be high for all vaccine types in any outbreak setting.<br>• Based on a few studies, VE for 1- and 2-dose recipients generally appeared to be similar, with slightly higher effectiveness for 2 doses. | | |
| | | **At least one-dose monovalent or quadrivalent MMRV** | Total: 17 studies<br><br>Surveillance (n=8);<br>Multiple cross-sectional (n=1);<br>Retrospective (n=4);<br>NR (n=4) | No vaccination | 4-10yrs (incidence)<br><br>5-15yrs after vaccine introduction (hospitalisation) | Incidence of varicella<br><br>Incidence of breakthrough varicella (BV)<br><br>Hospitalisation associated with varicella<br><br>Complications associated with varicella<br><br>Mortality associated with varicella | **Incidence of varicella** (n=9 studies)<br>• Included observational studies showed that varicella vaccination (and particularly routine varicella vaccination in infants) decreased varicella incidence by 34%-90% compared to pre-vaccination, over a period of 4-10 years. A strong decrease was observed particularly in children and adolescents.<br><br>**Hospitalisation associated with varicella** (n= 8 studies)<br>• After vaccine introduction or compared to pre-vaccination | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| Cochrane Library: 2000 to 2010 | | | | | | | status, varicella-related hospitalisations significantly declined by 43%-88% for all age groups, over a period of 5-15 years.<br>• No change was observed in the mean duration of hospital stay.<br><br>**Complications associated with varicella** (n=4 studies)<br>• After the introduction of varicella vaccination, the occurrence of varicella-related complications significantly decreased.<br><br>**Mortality associated with varicella** (n=1 study)<br>• During the 12 yrs of the mostly 1-dose US varicella vaccination program, the average age-adjusted mortality due to varicella as an underlying cause of death decreased 88% to 0.05/1 million population during the period 2005–2007 (p<0.001), with a reduction of 97% among persons <20yrs. | | |
| | | **At least one-dose monovalent or quadrivalent** (brand NR) | Total: 7 studies<br>Surveillance (n=6); Prospective cohort (n=1) | NA | NR | Proportion of BV | **Proportion of BV** (n=3 studies)<br>• Overall, proportions of BV in vaccinated groups vary between studies and years of observation. This may be related to vaccination coverage, the administered type or dose of vaccine, study population (e.g., age) or time since vaccination. | | |
| | | **At least one-dose monovalent or quadrivalent** (multiple brands) | Total: 23 studies<br>Study type: various | Age at vaccination | NR | Incidence of BV | **Incidence of BV**<br>• Younger age at vaccination (≤14-18 months) may be a risk factor for vaccine failure, but the evidence was not consistent.<br>• Children vaccinated at an age of ≤2yrs may be at lower risk for moderate/severe BV | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | compared with children vaccinated at an older age. | | |
| | | | | Time since vaccination | Up to 10yrs | | **Incidence of BV**<br>• Mild BV rates do not seem to increase over time since immunisation (<10 years) in children at risk of exposure.<br>• A few studies reported significant higher risk ratios for children vaccinated >5yrs ago compared to children immunised more recently.<br>• Evidence indicates that if BV occurs, moderate/severe cases are more often observed with increasing time since immunisation. | | |
| | | | Total: 3 studies<br>Study type: various | Co-administration with another vaccine (MMR) | NR | | **Incidence of BV**<br>• 1 study showed that varicella vaccine administration within 28 days of receipt of the MMR vaccine increases the risk for BV. | | |

Key: BV – breakthrough varicella; CoCanCPG - Coordination of Cancer Clinical Practice Guidelines; ECDC - European Centre for Disease Prevention and Control; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; NR – not reported; RCT – randomised controlled trial; SR – systematic review; VE – vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Skull<br><br>2001<br><br>10.1136/adc.85.2.83<br><br>Funding: NR<br><br>1966 to December 2000 | Human subjects vaccinated with VZV vaccine | **One-dose**<br>(vaccine type NR) | Total: 21 studies<br>RCTs (n=6)<br>Prospective cohort (n=14)<br>Post-licensure study (n=1) | Placebo and no vaccination | Up to 7yrs (1 RCT) | Vaccine effectiveness against varicella<br><br>Long-term persistence of protection against varicella<br><br>Attack rate<br><br>Risk of breakthrough varicella | **Vaccine efficacy/ effectiveness**<br>• 2 RCTs provide evidence that a single dose of VZV vaccine for children (aged 10mths to 14yrs) is effective in preventing varicella as follows:<br>o VE: 100% over 9mths and 98% over 7yrs (data beyond 3yrs subject to large loss to follow-up) (1 RCT)<br>o VE: 72% over a mean of 29mths (1 RCT)<br>o Attack rates in both RCTs were 0-3% per year in vaccinated group versus 7-11% in placebo group.<br>• A cohort study of vaccinated and unvaccinated children <5yrs old found a VE of 83%.<br>• Supporting evidence for vaccine effectiveness is provided by 3 more RCTs and 12 prospective cohort studies.<br>• For RCTs, attack rates were 0-3% per year in vaccinated group versus 7-11% in placebo group, giving the number needed to treat to prevent one case of varicella as 5.5–11.8. Assuming complications occur in 1% of varicella cases, the number needed to vaccinate to prevent one complicated case of varicella is therefore 550 to 1180.<br>• Supportive evidence of a low annual attack rate in vaccines (including children, adolescents and adults) is provided by other RCTs to 4yrs (0.3–3.6%), and prospective cohort studies to 19.6 years (0.3–2.8%). | This critical review has found strong evidence for the effectiveness of VZV vaccination in the prevention of varicella in children. | **Risk of bias**<br>Studies were systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care. The results for individual studies are not provided.<br>The quality of evidence in studies included in this analysis was reported as generally good. However, the following methodological issues were identified.<br><br>Loss of subjects from analysis was sometimes considerable, particularly where the duration of follow up was ≥7yrs. Other trials relied on self reporting of VZV disease to investigators, while occasional studies followed only vaccinees who initially seroconverted. |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • Breakthrough disease may be more common in individuals who are seronegative prior to vaccination. Exposure to varicella and <14mths of age at time of vaccination have also been shown to be risk factors for breakthrough disease. | | These biases could potentially result in an over estimation of VE by underestimating the true number of cases. However, outcomes across studies were consistent regardless of study design or duration of follow up, suggesting a true effect.<br>**Overall quality of evidence assessment**<br>Using the Canadian Task Force on Preventive Health Care methodology, there was deemed Good evidence to include immunisation of 12-15mth old children with varicella vaccine to prevent varicella infection and secondary cases in household contacts. This was based on Level I Evidence provided from 6 well designed RCTs and Level II-I Evidence from 12 well designed cohort studies. |

Key: NR - not reported; nRCT - non-randomised controlled trial;PCR - polymerase chain reaction; RCT - randomised controlled trial; VE - vaccine effectiveness; VZV - varicella zoster virus;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Xu<br><br>2019<br><br>10.13200/j.cnki.cjb.002616<br>http://www.cqvip.com/qk/97789x/20195/7002176336.html<br><br>Funding source not provided<br><br>Period before 2017 | Children and students in varicella outbreak clusters in China | **One-dose** (vaccine type NR) | Total: 3 studies<br>Study type: unclear | No vaccination | NR | Vaccine effectiveness for prevention of varicella | **Pooled VE against varicella (95% CI)**<br>(random effects model)<br>• Overall (n=3 estimates): VE 60% (42 to 73%, $I^2$=31%)¥ | Varicella immunisation has a certain protective effect, which decreases with the increase of vaccination age. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | Children and students in varicella outbreak clusters in China | **Two-dose** (vaccine type NR) | Total: 3 studies<br>Study type: unclear | No vaccination | NR | Vaccine effectiveness for prevention of varicella | **Pooled VE against varicella (95% CI)**<br>(random effects model)<br>• Overall (n=3 estimates): VE 92% (80 to 97%, $I^2$=0%)¥<br><br>¥Difference between VE of one-dose and two-dose statistically significant | | |
| | n=57,556 children and students in varicella outbreak clusters in China | **At least one-dose** (vaccine type NR) | Total: 34 studies<br>**Case-control** (n=19)<br>**Cohort** (n=15) | No vaccination | NR | Vaccine effectiveness for prevention of varicella<br><br>Long-term persistence of protection based on incidence of breakthrough varicella over time | **Pooled VE against varicella (95% CI)**<br>(random effects model)<br>• Overall (n=34 estimates): VE 69% (64 to 73%, $I^2$=69%)<br><br><u>By study design</u><br>• Case-control (n=19 estimates): VE 68% (61 to 74%, $I^2$=72%)<br>• Cohort (n=14 estimates): VE 71% (63 to 77%, $I^2$=65%)<br><br><u>By school</u><br>• Preschool (n= 2 estimates): VE 78% (60 to 87%, $I^2$=0%)‡<br>• Primary school (n=2 estimates): VE 33% (4 to 54%, $I^2$ = 0%)‡<br>‡Difference in VE between preschool and primary school children statistically significant (p<0.00001)<br><br><u>By current age (recommendation is vaccination once 12mths old)</u><br>• Overall (n=12 estimates): VE 79% (63 to 88%, $I^2$=89%)<br>• <5yrs old (n=3 estimates): VE 94% (69 to 99%, $I^2$=91%)<br>• <9yrs old (n=4 estimates): VE 87% (64 to 96%, $I^2$=88%)<br>• ≥9yrs old (n=5 estimates): VE 41% (23 to 54%, $I^2$=0%) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Meta-regression identified that study year, sample size and study methods may have affected heterogeneity (all p<0.0001). | | |

Key: CI – confidence interval; NR – not reported; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Yin<br><br>2018<br><br>doi.org/10.1080/14760584.2018.1433999<br><br>Natural Science Foundation of Guangdong Province, China<br><br>1995 to June 2017 | Immunocompetent children aged 12mths to 12yrs in USA and 10 European countries | **Two-dose monovalent or quadrivalent MMRV** (3wks-6mths between doses) | Total: 2 studies<br>**RCT** (n=2) | One-dose | 3-10yrs | Incremental vaccine efficacy (VE) against varicella‡<br>‡defined in this review as clinical and/or laboratory-confirmed | **Pooled incremental VE (95% CI) against <u>any severity varicella</u>** (random effects model)<br>• Overall (n=2 estimates):<br>VE 79% (56 to 90%, $I^2$=91.4%) | Two-dose vaccination provides superior protection against breakthrough varicella infection compared to one-dose vaccination. | **Risk of bias**<br>Risk of bias conducted for all primary studies. Quality scores showed that the quality of all RCTs was high and that the quality of all eligible case–control studies and retrospective cohort studies was ≥7 stars, indicating that the quality of these studies was also good. The modified NOS score of the self-control studies ranged from 5 to 6 stars.<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | Immunocompetent children (n=2,389) aged 12mths to 13yrs at day-care centers or schools that experienced outbreaks in America, Spain, China, and Germany | **Two-dose** (vaccine type NR) (coverage 10-67%) | Total: 7 studies<br>**Retrospective cohort** (n=7) | One-dose (coverage 31-90%) | NR | Incremental vaccine effectiveness (VE) against varicella | **Pooled incremental VE (95% CI) against <u>any severity varicella</u>** (random effects model)<br>• Overall (n=8 estimates):<br>VE 63% (36 to 79%, $I^2$=54.6%) | | |
| | | **Two-dose** (vaccine type NR) (coverage 39-67%) | Total: 2 studies<br>**Retrospective cohort** (n=2) | One-dose (coverage 31%-58%) | | Incremental vaccine effectiveness (VE) against <u>laboratory confirmed</u> varicella | **Pooled incremental VE (95% CI) against <u>any severity varicella</u>** (random effects model)<br>• Overall (n=3 estimates):<br>VE 42% (-0.01 to 67%, $I^2$=59.5%) | | |
| | | **Two-dose** (vaccine type NR) (coverage 10-65%) | Total: 5 studies<br>**Retrospective cohort** (n=5) | One-dose (coverage 35%-90%) | | Incremental vaccine effectiveness (VE) against <u>clinically diagnosed</u> varicella | **Pooled incremental VE (95% CI) against <u>any severity varicella</u>** (random effects model)<br>• Overall (n=5 estimates):<br>VE 80% (62 to 90%, $I^2$=0%) | | |
| | Immunocompetent children (n=1,547) aged 15mths to 18.7yrs in Connecticut (USA), West Virginia (USA), Spain, Germany, Antelope Valley (USA), Canada, Philadelphia, and Panama | **Two-dose** (vaccine type NR) | Total: 5 studies<br>**Case-control study** (n=5) | One-dose | NR | Incremental vaccine effectiveness (VE) against varicella - any severity | **Pooled incremental VE (95% CI) against <u>any severity varicella</u>** (random effects model)<br>• Overall (n=6 estimates):<br>VE 81% (65 to 90%, $I^2$=26.4%) | | |

Key: MMRV – measles, mumps, rubella, varicella; NR – not reported; VE - vaccine efficacy/effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Zhang<br><br>2020<br><br>10.3760/cma.j.cn112338-20191025-00762<br><br>Funding source not reported<br><br>Period before 2019 | Healthy children (n=328,565) aged 1-12yrs in China | **One-dose** (vaccine type NR) | Total: 32 studies<br>**Retrospective Cohort** (n=20)<br>**Prospective Cohort** (n=6)<br>**Case-control** (n=6) | No vaccination | NR | Vaccine effectiveness for prevention of varicella | **Pooled VE against varicella (95% CI)**<br>(random effects model)<br>• Overall (n=32 estimates): VE 75% (68 to 80%, $I^2$=83%)<br><br>By study design<br>• Cohort (n=26 estimates, n=323,123 children): VE 72% (65 to 80%, $I^2$=84%)<br>• Case-control (n=6 estimates, n=5,433 children): VE 78% (67 to 85%, $I^2$=78%)<br>By setting<br>• Outbreak (n=22 estimates, n=17,154 children): VE 66% (57 to 73%, $I^2$=62%)<br>• Non-outbreak (n=10 estimates, n=311,411 children): VE 85% (78 to 89%, $I^2$=87%)<br>By age of study participants<br>• <6yrs old (n=12 estimates, n=8,124 children): VE 84% (77 to 89%, $I^2$=59%)<br>• ≥6yrs old (n=19 estimates, n=16,488 children): VE 60% (51 to 68%, $I^2$=55%)<br>By NOS quality score<br>• ≥5 (n=20 estimates, n=19,890 children): VE 74% (71 to 77%, $I^2$=78%)<br>• <5 (n=12 estimates, n=305,536 children): VE 76% (63 to 85%, $I^2$=86%) | One-dose of live attenuated varicella vaccine in healthy children aged 1-12yrs in China can provide moderate protection, but the VE of children ≥6yrs is significantly reduced. | **Risk of bias**<br>Conducted for all primary studies using NOS. Scores ranged from 4 to 8 (out of a possible 9), of which 20/32 (62%) studies scored ≥5 and 12 studies (38%) scored <5. Those with a score <5 were considered at higher risk of bias.<br><br>**Overall quality of evidence assessment**<br>GRADE quality of evidence assessment was undertaken and the quality of evidence of pooled one-dose VE was assessed as VERY LOW. |

Key: CI – confidence interval; GRADE - Grading of Recommendations Assessment, Development and Evaluation; NOS – Newcastle Ottawa Scale; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Zhang<br><br>2021<br><br>10.1186/s12879-021-06217-1<br><br>Beijing Natural Science Foundation, China<br><br>1997 to September 2019 | Healthy children (n=87,196) aged 2-12yrs in China in the following settings: Elementary school (n=9 studies), Kindergarten and elementary school (n=1), Community (n=2) | **Two-dose** (vaccine type NR) (vaccine brand named in 1 study only – produced by Beijing Tiantan biological products corporation limited) | Total: 12<br>**Retrospective cohort** (n=11)<br>**Prospective cohort** (n=1) | No vaccination | Unknown | Vaccine effectiveness (VE) against varicella | **Overall pooled VE (95% CI) against varicella**<br>(random effects model)<br>• Overall (n=12 estimates):<br>VE 90% (69 to 97%, $I^2$=83%) | Available data from China showed that the VE of the two-dose varicella vaccine is relatively high. | **Risk of bias**<br>Risk of bias was conducted for primary studies. The overall median quality score was 6.6 (4-8). Nine studies (75%) scored ≥7, which indicated high quality, while three studies (25%) scored 4–6, indicating intermediate quality.<br><br>**Overall quality of evidence assessment**<br>GRADE quality of evidence assessment was undertaken. Overall, the evidence quality assessment of the pooled two-dose VE was LOW.<br><br>The quality of evidence assessment of the pooled VE of subgroups |
| | Healthy children (n=83,560) aged 2-12yrs in China in a non-outbreak community setting (n=2 studies) | | Total: 2<br>**Retrospective cohort** (n=1)<br>**Prospective cohort** (n=1) | | | Vaccine effectiveness (VE) against varicella in non-outbreak settings | **Pooled VE (95% CI) against varicella <u>in non-outbreak settings</u>**<br>(fixed effects model)<br>• Overall (n=2 estimates):<br>VE 99% (98 to 99%, $I^2$=34%) | | |
| | Healthy children (n=3,636) aged 2-12yrs in China in the following outbreak settings: Elementary school (n=9 studies), kindergarten and elementary school (n=1) | | Total: 10<br>**Retrospective cohort** (n=10) | | | Vaccine effectiveness (VE) against varicella in outbreak settings | **Pooled VE (95% CI) against varicella <u>in outbreak settings</u>**<br>(fixed effects model)<br>• Overall (n=10 estimates):<br>VE 87% (76 to 93%, $I^2$=0%) | | |
| | Healthy children (n=86,367) aged 2-12yrs in China in the following settings: Elementary school (n=7 studies), Kindergarten and elementary school (n=1), Community (n=1) | | Total: 9 studies scoring ≥7 on NOS<br>**Retrospective cohort** (n=9) | | | Vaccine effectiveness (VE) against varicella | **Pooled VE (95% CI) against varicella <u>for studies scoring ≥7 on NOS</u>**<br>(random effects model)<br>• Overall (n=9 estimates):<br>VE 90% (60 to 97%, $I^2$=82%) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | Healthy children (n=829) aged 2-12yrs in China in the following settings: Elementary school (n=2 studies), Community (n=1 study) | | Total: 3 studies scoring <7 on NOS<br>**Retrospective cohort** (n=2)<br>**Prospective cohort** (n=1) | | | Vaccine effectiveness (VE) against varicella | **Pooled VE (95% CI) against varicella for studies scoring <7 on NOS**<br>(fixed effects model)<br>• Overall (n=3 estimates):<br>VE 88% (71 to 95%, $I^2$=0%) | | with an NOS score ≥7 was assessed as MODERATE. It was assessed as LOW in subgroups with an NOS score <7. |

Key: CI - confidence interval; NOS - Newcastle Ottawa Scale; NR - not reported; VE - vaccine efficacy/effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Zhu<br><br>2017<br><br>10.16506/j.1009-6639.2017.08.008<br><br>Hangzhou Municipal Health Science and Technology Program Project (2016B46)<br><br>1998 to March 2016 | Children (n=421,189) aged 0-18yrs in China<br><br>Community, kindergarten, primary school, junior high school, secondary school, and rehabilitation centre settings | **One-dose** (vaccine type NR) | Total: 35 studies<br>**Cohort** (n=6)<br>**Case-control** (n=28)<br>**Cross-sectional** (n=1) | No vaccination | NR | Vaccine effectiveness for prevention of varicella | **Pooled VE against varicella (95% CI)**<br>(random effects model)<br>• Overall (n=35 estimates): VE 75% (68 to 80%, $I^2$=90.7%)<br><br>By study type<br>• Cohort (n=6 estimates, n=300,608 children): VE 88% (82 to 92%, $I^2$=NR)<br>• Case-control (n=28 estimates, n=119,443 children): VE 67% (59 to 73%, $I^2$=NR)<br>By schooling status<br>• Pre-school/≤6yrs (n=10 estimates, n=61,256 children): VE 90% (81 to 95%, $I^2$=NR)<br>• Primary school (n=17 estimates, n=11,574 children): VE 67% (52 to 78%, $I^2$=NR)<br>By vaccine<br>• Imported (n=6 estimates, n=16,146 children): VE 75% (63 to 83%, $I^2$=NR)<br>• Domestic (n=10 estimates, n=275,901 children): VE 79% (71 to 85%, $I^2$=NR)<br>By setting<br>• Outbreak in collective institution (n=17 estimates, n=13,352 children): VE 59% (47 to 68%, $I^2$=NR) | Live attenuated varicella vaccine is moderately effective in preventing varicella, but the VE reduces over time. | **Risk of bias**<br>Conducted for all primary studies using NOS. Scores ranged from 4 to 7 (out of a possible 9). 25/35 (71%) studies scored ≥6 and 10 studies (29%) scored <6. A score of at least 6 indicated high quality research.<br><br>**Overall quality of evidence assessment**<br>Not conducted |

Key: CI - confidence interval; NOS - Newcastle Ottawa Scale; NR - not reported; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Zhu<br><br>2018<br><br>10.1016/j.ajic.2017.07.029<br><br>Funding source NR<br><br>(No start date reported)<br>30 September 2016 | n=27,618 breakthrough varicella cases in healthy children aged 9mths to 17yrs from studies in the following countries:<br>Canada (n=1 study);<br>China (n=2);<br>Germany, Belgium & Netherlands (n=1);<br>Israel (n=1);<br>Italy (n=1);<br>Japan (n=2);<br>Singapore (n=1);<br>Taiwan (n=2);<br>Turkey (n=1);<br>USA (n=12) | **One-dose monovalent or quadrivalent MMRV**<br>(various vaccines)<br>Varivax (n=11);<br>Varilrix (n=4);<br>Okavax (n=2 studies);<br>Not available (n=2);<br>MMRV (n=1);<br>MMR II and Varivax (n=1);<br>Oka strain (n=1);<br>Varivax and Varilrix (n=1);<br>Changchun (n=1); | Total: 24 studies (30 study populations)<br>**RCT** (n=4)<br>**Prospective cohort** (n=17)<br>**Retrospective cohort** (n=2)<br>**Computer system-based** (n=7) | No vaccination or no control group | 11mths to 14yrs | Incidence of breakthrough varicella (BV) | **Pooled average BV incidence rate. Cases per 1,000 person years (95% CI)**<br>(random effects model, unless otherwise stated)<br>• Overall: 8.5 (5.3 to 13.7, $I^2$=99.8%)<br><br>By vaccine type<br>• Varivax (n=14 study populations): 13.9 (11.1 to 17.4, $I^2$=96%)<br>• Varilrix (n=4 study populations): 28.2 (13.7 to 58.0, $I^2$=98.9%)<br>• Other monovalent: (n=3 study populations): 3.2 (1.5 to 7.0, $I^2$=99.5%)<br>• Quadrivalent MMRV (n=3 study populations): 3.2 (0.7 to 15.4, $I^2$=77.1%)<br><br>By study design<br>• RCT (n=4 study populations, fixed effects model) 6.5 (4.5 to 9.4, $I^2$=0%)<br>• Prospective cohort (n=17 study populations): 14.9 (10.5 to 21.1, $I^2$=98.8%)<br>• Retrospective cohort (n=2 study populations): 41.1 (18.7 to 90.4, $I^2$=97.7%)<br>• Computer based/system studies (n= 7 study populations): 1.7 (0.93 to 3.0, $I^2$=99.4%)<br><br>By region<br>• Asia (n=12 study populations): 5.1 (2.4 to 10.9, $I^2$=99.8%)<br>• North America (n=15 study populations): 15.5 (12.1 to 19.8, $I^2$=96.9%)<br>• Europe (n=3 study populations): 3.2 (0.7 to 15.4, $I^2$=77.1%)<br><br>By age at vaccination | Two doses of varicella vaccine are more effective than a single dose, and 3-4 years between the first and second vaccinations may achieve higher efficacy. | **Risk of bias**<br>Risk of bias was conducted for primary studies. An adjusted NOS was used with possible scores ranging from 0-6. Individual study scores not provided.<br>Summary: 20% scored 4, 63% scored 5, and 17% scored 6.<br><br>**Overall quality of evidence assessment**<br>Not conducted |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • ≤2yrs (n=13 study populations): 4.7 (2.2 to 9.8, $I^2$=99.9%)<br>• >2yrs (n=6 study populations): 18.7 (10.7 to 32.8, $I^2$=98.1%)<br>• Mixed age (n=11 study populations): 10.6 (4.7 to 23.9, $I^2$=99.5%)<br><br>By NOS score<br>• NOS = 4 (n=6 study populations): 15.8 (9 to 27.5, $I^2$=98.2%)<br>• NOS=5 (n= 19 study populations): 5.5 PY (3 to 10.1, $I^2$=99.8%)<br>• NOS=6 (n=5 study populations): 18.7 PY (12.6 to 27.6, $I^2$=83.6%)<br>Results of the meta-regression showed that design type, type of vaccine, and their interaction had the most pronounced effects on the pooled average BV incidence rate and accounted for approximately 71.74% of the heterogeneity.<br>**Pooled annual BV incidence rate. Cases per 1,000 person years (95% CI)**<br>By time since vaccination<br>• 1st yr after (n=14 study populations): 13.2 (7.2 to 24.08, $I^2$=96.4%)<br>• 2nd yr after (n=12 study populations): 28.0 (1.6 to 53.7, $I^2$=95.1%)<br>• 3rd yr after: (n=9 study populations): 15.0 (5.8 to 39.1, $I^2$=94.6%)<br>• 4th yr after: (n=10 study populations): 35.3 (17.6 to 71.1, $I^2$=93.2)<br>• 5th yr after: (n=7 study populations): 23.7 (7.3 to 77.5, $I^2$=96.8)<br>• 6th yr after: (n=6 study populations): 24.7 (5.1 to 119.5, $I^2$=97.5)<br>• 7th yr after: (n=4 study populations): 10.5 (0.4 to 266.4, $I^2$=97.9%)<br>• 8th yr after (n=4 study populations): 32.3 (2.4 to 427.1, $I^2$=96.8%) | | |
| | n=24 breakthrough varicella cases in healthy children aged 1-12yrs from studies in the following countries: | **Two-dose monovalent or quadrivalent** (various vaccines for 5 study populations) MMRV (n=1); MMRV+4w (n=1); | Total: 4 studies (5 study populations) RCT (n=3) Prospective cohort (n=2) | Not vaccinated or no control | 13.5mths to 10yrs | Incidence of breakthrough varicella (BV) | **Pooled average BV incidence rate. Cases per 1,000 person years (95% CI)** (random effects model)<br>• Overall (n= 5 study populations): 2.2 (0.5 to 9.3, $I^2$=86.3%) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | Germany and Austria (n=1 study);<br>Germany, Belgium & Netherlands (n=1);<br>USA (n=2) | MMR+Varilrix (n=1)<br>Unknown (n=2) | | | | | | | |

Key: BV – breakthrough varicella; CI – confidence interval; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; MMRV+4w – measles, mumps, rubella, varicella with 4 week interval between doses; NOS – Newcastle Ottawa Scale; NR – not reported; PY – person years; VE - vaccine efficacy/effectiveness;

# Appendix A4.3 AMSTAR2 Quality Appraisal

| Review | Qu 1 | Qu 2 | Qu 3 | Qu 4 | Qu 5 | Qu 6 | Qu 7 | Qu 8 | Qu 9 | | Qu 10 | Qu 11 | | Qu 12 | Qu 13 | Qu 14 | Qu 15 | Qu 16 | Overall Quality Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Review Author & Year | Did the research questions and inclusion criteria for the review include the components of PICO? | Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Did the review authors explain their selection of the study designs for inclusion in the review? | Did the review authors use a comprehensive literature search strategy? | Did the review authors perform study selection in duplicate? | Did the review authors perform data extraction in duplicate? | Did the review authors provide a list of excluded studies and justify the exclusions? | Did the review authors describe the included studies in adequate detail? | Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | | Did the review authors report on the sources of funding for the studies included in the review? | If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | | If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? | Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | |
| AlKaabi_2020 | Yes | No | Yes | No | No | No | No | No | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Arlant_2019 | Yes | No | Yes | Partial Yes | No | No | No | Yes | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Bayer_2007 | Yes | No | No | Partial Yes | Yes | No | No | No | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No | No | No | No | Yes | No | Critically Low |
| Benchimol_20 | Yes | No | Yes | Partial Yes | Yes | Yes | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| DiPietrantonj_ | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | RCTs: Yes | NRSI: Yes | Yes | RCTs: Yes | NRSI: Yes | Yes | Yes | No | Yes | Yes | High |
| Garrido_2012 | Yes | No | No | No | No | No | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | Yes | No | No MA | Yes | Critically Low |
| Goh_2019 | Yes | No | Yes | Partial Yes | No | No | No | No | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Hong_2017 | Yes | No | Yes | Partial Yes | Yes | Yes | No | No | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No | No | No | Yes | Yes | No | Critically Low |
| Kaufmann_202 | Yes | Yes | Yes | Yes | Yes | Yes | No | No | RCTs: NA | NRSI: Partial Yes | No | RCTs: No MA | NRSI: No MA | No MA | Yes | No | No MA | Yes | Low |
| Marin_2016 | Yes | No | Yes | Partial Yes | No | No | No | Partial Yes | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: Yes | No | Yes | Yes | Yes | Yes | Critically Low |
| Meszner_2019 | Yes | No | Yes | No | Yes | No | No | Partial Yes | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| NZ_2012 | Yes | No | Yes | Partial Yes | No | No | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Pallas_2011 | Yes | No | Yes | No | Yes | Yes | Yes | Yes | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | Yes | No MA | No | Critically Low |
| Skull_2001 | Yes | No | Yes | Partial Yes | No | No | No | No | RCTs: No | NRSI: NA | No | RCTs: No MA | NRSI: No MA | No MA | Yes | No | No MA | Yes | Critically Low |
| Xu_2019 | Yes | No | No | No | Yes | Yes | No | No | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No | No | No | Yes | Yes | No | Critically Low |
| Yin_2018 | Yes | No | Yes | Partial Yes | Yes | Yes | No | No | RCTs: Partial Yes | NRSI: Partial Yes | No | RCTs: Yes | NRSI: Yes | Yes | Yes | Yes | Yes | Yes | Critically Low |
| Zhang_2020 | Yes | No | No | Partial Yes | Yes | Yes | No | Partial Yes | RCTs: NA | NRSI: Partial Yes | Yes | RCTs: No MA | NRSI: No | Yes | Yes | Yes | Yes | Yes | Critically Low |
| Zhang_2021 | Yes | No | No | Partial Yes | Yes | Yes | No | Partial Yes | RCTs: NA | NRSI: Partial Yes | No | RCTs: No MA | NRSI: No | Yes | Yes | Yes | Yes | Yes | Critically Low |
| Zhu_2017 | Yes | No | No | No | Yes | Yes | No | Partial Yes | RCTs: NA | NRSI: Partial Yes | No | RCTs: No MA | NRSI: No | No | No | No | Yes | No | Critically Low |
| Zhu_2018 | Yes | No | Yes | Partial Yes | Yes | Yes | No | Partial Yes | RCTs: No | NRSI: Partial Yes | No | RCTs: No | NRSI: No | Yes | No | Yes | Yes | Yes | Critically Low |

Key: MA – meta-analysis; NRSI – non-randomised study of intervention; RCT – randomised controlled trial;

## Appendix A4.4 Excluded studies

| Study Number | Title | Authors | Year Published | DOI / Weblink | Exclusion reason |
|---|---|---|---|---|---|
| 1 | Risk of febrile convulsions after mmrv vaccination in comparison to MMR or MMR + V vaccination | Schink, T.; Holstiege, J.; Edeltraut, G. | 2012 | 10.1002/pds.3324 | Abstract only |
| 2 | Varicella vaccination is associated with increased prevalence of eczema in the US | Silverberg, J.; Li, J. C. | 2015 | 10.1038/jid.2015.70 | Abstract only |
| 3 | The relation between vaccinations and optic neuritis-A literature review | Mailand, M. T.; Frederiksen, J. L. | 2017 | 10.1080/01658107.2017.1353798 | Abstract only |
| 4 | Severe complications of varicella in persons vaccinated with varicella vaccine (breakthrough varicella): A systematic literature review | Leung, J.; Broder, K.; Marin, M. | 2016 | 10.1093/ofid/ofw172.659 | Abstract only |
| 5 | Should varicella vaccination be introduced into the national immunization guidelines? | Nguyen, E.; Baird, O.; Dzulkarnain, M.; Wong, K.; Ali-Bujang, N.; Ooi, S. T.; Kivlehan, R.; Power, C.; Molloy, E.; Meehan, J. | 2019 | 10.1136/archdischild-2019-epa.715 | Abstract only |
| 6 | Varicella vaccination in The United States: Two decades of experience with program implementation | Marin, M.; Lopez, A. S.; Leung, J.; Schmid, D. S.; Harpaz, R. | 2016 | 10.1093/ofid/ofw172.620 | Abstract only |
| 7 | Should varicella vaccination be added to the UK immunisation schedule for healthy children? | Grey, S. J. | 2017 | 10.1136/archdischild-2017-313087.141 | Abstract only |
| 8 | 124 CANADIAN ASSOCIATION OF GASTROENTEROLOGY CLINICAL PRACTICE GUIDELINES ON IMMUNIZATIONS IN INFLAMMATORY BOWEL DISEASE | Benchimol, E. I.; Tse, F.; Carroll, M.; deBruyn, J.; McNeil, S. A.; Pham-Huy, A.; Seow, C. H.; Barrett, L.; Bessissow, T.; Carman, N.; Melmed, G.; Vanderkooi, O.; Marshall, J. K.; Jones, J. L. | 2020 | 10.1016/S0016-5085(20)30738-1 | Abstract only |
| 9 | Acute posterior multifocal placoid pigment epitheliopathy after vaccination: Review of the literature and analysis of the French Pharmacovigilance database | Mangavelle, J.; Damin-Pernik, M.; Bellet, F.; Abadie, D.; Pageot, C.; Beyens, M. N. | 2018 | 10.1111/fcp.12371 | Abstract only |
| 10 | Canadian association of gastroenterology clinical practice guidelines on immunizations in inflammatory bowel disease | Benchimol, E.; Tse, F.; Carroll, M.; DeBruyn, J.; McNeil, S.; Pham-Huy, A.; Seow, C.; Barrett, L.; Bessissow, T.; Carman, N.; Melmed, G.; Vanderkooi, O.; Marshall, J.; Jones, J. | 2021 | 10.1097/MPG.0000000000003177 | Abstract only |

| | | | | | |
|---|---|---|---|---|---|
| 11 | Vaccines and Optic Neuritis: A systematic review | Frederiksen, J. L. | 2018 | https://onlinelibrary.wiley.com/doi/epdf/10.1111/ene.13699 | Abstract only |
| 12 | Safety of Vaccines Used for Routine Immunization in the United States: An update | Aneesa Motala, Susanne Hempel Courtney Gidengil Matthew Goetz Margaret Maglione Owen Hall Jody Larkin Sydne Newberry Christine Chen Nabeel Qureshi Goke Akinniranye | 2020 | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020180089 | Duplicate |
| 13 | Varicella and rotovirus vaccination in New Zealand - assessment reports | New Zealand National Health Committee | 2012 | http://nhc.health.govt.nz/varicella-and-rotovirus-vaccination-new-zealand-assessment-reports | Duplicate |
| 14 | Meta analysis of vaccine effectiveness in varicella outbreaks | Bayer, O; Heininger, U; Heiligensetzer, C; von Kries, R | 2007 | 10.1016/j.vaccine.2007.07.010 | Duplicate |
| 15 | Varicella vaccination in Italy: an economic evaluation of different scenarios | Coudeville, L; Brunot, A; Giaquinto, C; Lucioni, C; Dervaux, B | 2012 | 10.2165/00019053-200422130-00003 | Duplicate |
| 16 | Vaccination recommendations for Germany | Wiese-Posselt, Miriam; Tertilt, Christine; Zepp, Fred | 2011 | 10.3238/arztebl.2011.0771 | Not a systematic review |
| 17 | Varicella: Efficacy of two-dose vaccination in childhood | Wutzler, P.; Knuf, M.; Liese, J. | 2008 | 10.3238/arztebl.2008.0567 | Not a systematic review |
| 18 | Universal varicella vaccine immunization in Japan | Yoshikawa, Tetsushi; Kawamura, Yoshiki; Ohashi, Masahiro | 2016 | 10.1016/j.vaccine.2016.02.058 | Not a systematic review |
| 19 | Increasing coverage and efficiency of measles, mumps, and rubella vaccine and introducing universal varicella vaccination in Europe: a role for the combined vaccine | Vesikari, Timo; Sadzot-Delvaux, Catherine; Rentier, Bernard; Gershon, Anne | 2007 | 10.1097/INF.0b013e3180616c8f | Not a systematic review |
| 20 | Global impact of varicella vaccination programs | Varela, Fernanda Hammes; Pinto, Leonardo Arajuo; Scotta, Marcelo Comerlato | 2019 | 10.1080/21645515.2018.1546525 | Not a systematic review |
| 21 | Development of varicella vaccine in Japan and future prospects | Ozaki, Takao; Asano, Yoshizo | 2016 | 10.1016/j.vaccine.2016.04.059 | Not a systematic review |
| 22 | Herpes zoster virus sclerokeratitis and anterior uveitis in a child following varicella vaccination | Naseri, A.; Good, W. V.; Cunningham Jr, E. T. | 2003 | 10.1016/S0002-9394(02)01957-8 | Not a systematic review |
| 23 | Varicella vaccination in Australia | Macartney, KK; Beutels, P; McIntyre, P; Burgess, MA | 2005 | 10.1111/j.1440-1754.2005.00717.x | Not a systematic review |

| | | | | | |
|---|---|---|---|---|---|
| 24 | Varicella | Heininger, Ulrich; Seward, Jane F | 2006 | 10.1016/S0140-6736(06)69561-5 | Not a systematic review |
| 25 | Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine and Commonly Administered Vaccines After Coadministration | Gasparini, Roberto; Tregnaghi, Miguel; Keshavan, Pavitra; Ypma, Ellen; Han, Linda; Smolenov, Igor | 2016 | 10.1097/INF.0000000000000930 | Not a systematic review |
| 26 | The safety profile of varicella vaccine: a 10-year review | Galea, Susan A; Sweet, Ann; Beninger, Paul; Steinberg, Sharon P; LaRussa, Philip S; Gershon, Anne A; Sharrar, Robert G | 2008 | 10.1086/522125 | Not a systematic review |
| 27 | Varicella-zoster virus infection: natural history, clinical manifestations, immunity and current and future vaccination strategies | Freer, Giulia; Pistello, Mauro | 2018 | http://www.newmicrobiologica.org/PUB/allegati_pdf/2018/2/95.pdf | Not a systematic review |
| 28 | Review of the Varilrix™ varicella vaccine | Chiu, SS.; Lau, YL. | 2005 | 10.1586/14760584.4.5.629 | Not a systematic review |
| 29 | A literature review regarding the management of varicella-zoster virus | Bond, D.; Mooney, J. | 2010 | 10.1002/msc.175 | Not a systematic review |
| 30 | Live attenuated varicella vaccine | Arvin, Ann M; Gershon, Anne A | 1996 | 10.1146/annurev.micro.50.1.59 | Not a systematic review |
| 31 | Varicella infection in the Middle East: Prevalence, complications, and vaccination | Al-Turab, Mariam; Chehadeh, Wassim | 2018 | 10.4103/jrms.JRMS_979_17 | Not a systematic review |
| 32 | Twelve children with varicella vaccine meningitis: Neuropathogenesis of reactivated live attenuated varicella vaccine virus | Heusel, E. H.; Grose, C. | 2020 | 10.3390/v12101078 | Not a systematic review |
| 33 | Cutaneous adverse reactions following anti-infective vaccinations | Nikkels, A. F.; Nikkels-Tassoudji, N.; PiÃ©rard, G. E. | 2005 | 10.2165/00128071-200506020-00002 | Not a systematic review |
| 34 | Preventing varicella-zoster disease | Hambleton, Sophie; Gershon, Anne A | 2005 | 10.1128/CMR.18.1.70-80.2005 | Not a systematic review |
| 35 | Varicella vaccination of children in the United States: assessment after the first decade 1995-2005 | Grose, Charles | 2005 | 10.1016/j.jcv.2005.02.003 | Not a systematic review |
| 36 | Recommendation on the Use of the Chicken pox Vaccine in Belgium | Conseil supérieur d'Hygiène | 2005 | https://www.nitag-resource.org/sites/default/files/2c1eb376d94d1c96b0ccfc57d206acd7f2c35ecb_1.pdf | Not a systematic review |

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| 37 | Varicella infections and varicella vaccine in the 21st century | Vazquez, Marietta | 2004 | 10.1097/01.inf.0000140786.15816.38 | Not a systematic review |
| 38 | Update on varicella | Seward, Jane F | 2001 | 10.1097/00006454-200106000-00014 | Not a systematic review |
| 39 | Live-attenuated varicella vaccine | Gershon, Anne A | 2001 | 10.1016/s0891-5520(05)70268-3 | Not a systematic review |
| 40 | Varicella vaccine: genesis, efficacy, and attenuation | Arvin, Ann M | 2001 | 10.1006/viro.2001.0918 | Not a systematic review |
| 41 | Uveitis associated with varicella virus vaccine | Esmaeli-Gutstein, B.; Winkelman, J. Z. | 1999 | 10.1016/S0002-9394(99)00059-8 | Not a systematic review |
| 42 | Varicella vaccines | Flatt, A.; Breuer, J. | 2012 | 10.1093/bmb/lds019 | Not a systematic review |
| 43 | Varicella-zoster virus | Arvin, Ann M | 1996 | 10.1128/cmr.9.3.361 | Not a systematic review |
| 44 | Varicella vaccine: the Japanese experience | Asano, Yoshizo | 1996 | 10.1093/infdis/174.supplement_3.s310 | Not a systematic review |
| 45 | CAVEI recommendation for the introduction of varicella vaccine into the National Immunization Programme | CAVEI | 2020 | 10.4067/s0716-10182020000200149 | Not a systematic review |
| 46 | Vaccine associated uveitis | Benage, M.; Fraunfelder, R. W. | 2015 | https://iovs.arvojournals.org/article.aspx?articleid=2335858 | Not a systematic review |
| 47 | Varicella vaccination in Europe - taking the practical approach | Bonanni, Paolo; Breuer, Judith; Gershon, Anne; Gershon, Michael; Hryniewicz, Waleria; Papaevangelou, Vana; Rentier, Bernard; Rumke, Hans; Sadzot-Delvaux, Catherine; Senterre, Jacques | 2009 | 10.1186/1741-7015-7-26 | Not a systematic review |

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| 48 | Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: a pooled analysis of r | Bryant, Kristina; McVernon, Jodie; Marchant, Colin; Nolan, Terry; Marshall, Gary; Richmond, Peter; Marshall, Helen; Nissen, Michael; Lambert, Stephen; Aris, Emmanuel; Mesaros, Narcisa; Miller, Jacqueline | 2012 | 10.4161/hv.20357 | Not a systematic review |
| 49 | The effect of vaccination on the epidemiology of varicella zoster virus | Edmunds, WJ; Brisson, M | 2002 | 10.1053/jinf.2002.0988 | Not a systematic review |
| 50 | Pathogenesis and current approaches to control of varicella-zoster virus infections | Gershon, Anne A; Gershon, Michael D | 2013 | 10.1128/CMR.00052-13 | Not a systematic review |
| 51 | Varicella vaccine: the American experience | Gershon, Anne A; LaRussa, Philip; Hardy, Iain; Steinberg, Sharon; Silverstein, Saul | 1992 | https://www.jstor.org/stable/30111789 | Not a systematic review |
| 52 | Sixteen years of global experience with the first refrigerator-stable varicella vaccine (Varilrix™) | Kreth, H. W.; Lee, B. W.; Kosuwon, P.; Salazar, J.; Gloriani-Barzaga, N.; Bock, H. L.; Meurice, F. | 2008 | 10.2165/0063030-200822060-00005 | Not a systematic review |
| 53 | Varicella vaccine strain infection in a non-immunocompromised patient. A case report and review of literature | Swed-Tobia, Rana; Kassis, Imad; Hanna, Suhair; Szwarcwort-Cohen, Moran; Dovrat, Sara; Dabaja-Younis, Halima | 2021 | 10.1080/21645515.2020.1802976 | Not a systematic review |
| 54 | Long-term clinical studies of varicella vaccine at a regional hospital in Japan and proposal for a varicella vaccination program | Ozaki, Takao | 2013 | 10.1016/j.vaccine.2013.10.060 | Not a systematic review |
| 55 | Varicella vaccination in Japan: necessity of implementing a routine vaccination program | Ozaki, Takao | 2013 | 10.1007/s10156-013-0577-x | Not a systematic review |
| 56 | Consensus: varicella vaccination of healthy children: a challenge for Europe | Rentier, Bernard; Gershon, Anne A | 2004 | 10.1097/01.inf.0000122606.88429.8f | Not a systematic review |
| 57 | Impact of varicella vaccine on varicella-zoster virus dynamics | Schmid, D Scott; Jumaan, Aisha O | 2010 | 10.1128/CMR.00031-09 | Not a systematic review |
| 58 | Pediatric Wells syndrome (eosinophilic cellulitis) after vaccination: A case report and review of the literature | Yu, A. M.; Ito, S.; Leibson, T.; Lavi, S.; Fu, L. W.; Weinstein, M.; Skotnicki, S. M. | 2018 | 10.1111/pde.13532 | Not a systematic review |

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| 59 | Successes and challenges in varicella vaccine | Papaloukas, Orestis; Giannouli, Georgia; Papaevangelou, Vassiliki | 2014 | 10.1177/2051013613515621 | Not a systematic review |
| 60 | Varicella and herpes zoster vaccine development: lessons learned | Warren-Gash, Charlotte; Forbes, Harriet; Breuer, Judith | 2017 | 10.1080/14760584.2017.1394843 | Not a systematic review |
| 61 | Varicella vaccination - the global experience | Wutzler, Peter; Bonanni, Paolo; Burgess, Margaret; Gershon, Anne; Safadi, Marco Aurelio; Casabona, Giacomo | 2017 | 10.1080/14760584.2017.1343669 | Not a systematic review |
| 62 | Chickenpox | Breuer, Judith; Fifer, Helen | 2011 | https://pubmed.ncbi.nlm.nih.gov/21486500/ | Not a systematic review |
| 63 | Varicella-zoster virus: pathogenesis, incidence patterns and vaccination programs | Gabutti, Giovanni; Franchi, Michele; Maniscalco, Licia; Stefanati, Armando | 2016 | https://www.minervamedica.it/en/journals/minerva-pediatrics/article.php?cod=R15Y2016N03A0213 | Not a systematic review |
| 64 | Epidemiologic effects of varicella vaccination | Halloran, M Elizabeth | 1996 | 10.1016/S0891-5520(05)70318-4 | Not a systematic review |
| 65 | NACI Statement on measles-mumps-rubella-varicella vaccine - September 2010 | Immunization, National Advisory Committee on | 2010 | https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2010-36/canada-communicable-disease-report-14.html | Not a systematic review |
| 66 | Severe varicella in persons vaccinated with varicella vaccine (breakthrough varicella): a systematic literature review | Leung, J.; Broder, K. R.; Marin, M. | 2017 | 10.1080/14760584.2017.1294069 | Not a systematic review |
| 67 | Vaccine schedules and procedures, 2007 | Middleton, D. B.; Zimmerman, R. K.; Mitchell, K. B. | 2007 | https://pubmed.ncbi.nlm.nih.gov/17270110/ | Not a systematic review |
| 68 | Immunizations, neonatal jaundice and animal-induced injuries | Post, J. N. | 2006 | 10.1097/01.mop.0000193315.52957.e3 | Not a systematic review |
| 69 | Effectiveness of live varicella vaccine | Takahashi, Michiaki | 2004 | 10.1517/14712598.4.2.199 | Not a systematic review |
| 70 | Varicella zoster virus infections in children after the introduction of live attenuated varicella vaccine | Vazquez, Marietta | 2004 | 10.1097/00008480-200402000-00015 | Not a systematic review |

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| 71 | Routine vaccines across the life span, 2007 | Zimmerman, R. K.; Middleton, D. B.; Burns, I. T.; Clover, R. D.; Kimmel, S. R. | 2007 | https://pubmed.ncbi.nlm.nih.gov/17270108/ | Not a systematic review |
| 72 | Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States | Halloran, M. E.; Cochi, S. L.; Lieu, T. A.; Wharton, M.; Fehrs, L. | 1994 | 10.1093/oxfordjournals.aje.a117238 | Not a systematic review |
| 73 | International Consensus (ICON): Allergic reactions to vaccines | Dreskin, S. C.; Halsey, N. A.; Kelso, J. M.; Wood, R. A.; Hummell, D. S.; Edwards, K. M.; Caubet, J. C.; Engler, R. J. M.; Gold, M. S.; Ponvert, C.; Demoly, P.; Sanchez-Borges, M.; Muraro, A.; Li, J. T.; Rottem, M.; Rosenwasser, L. J. | 2016 | 10.1186/s40413-016-0120-5 | Not a systematic review |
| 74 | Trends in varicella epidemiology before and after the implementation of universal one-dose varicella vaccination | Lai, S. W. | 2019 | 10.1080/21645515.2019.1633879 | Not a systematic review |
| 75 | Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004-2009 | Williams, S. E.; Klein, N. P.; Halsey, N.; Dekker, C. L.; Baxter, R. P.; Marchant, C. D.; LaRussa, P. S.; Sparks, R. C.; Tokars, J. I.; Pahud, B. A.; Aukes, L.; Jakob, K.; Coronel, S.; Choi, H.; Slade, B. A.; Edwards, K. M. | 2011 | 10.1016/j.vaccine.2011.07.044 | Not a systematic review |
| 76 | The current status of live attenuated varicella vaccine | Gershon, AA | 2001 | 10.1007/978-3-7091-6259-0_1 | Not a systematic review |
| 77 | Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines | Schattner, Ami | 2005 | 10.1016/j.vaccine.2005.03.005 | Not a systematic review |
| 78 | [Varicella disease and varicella vaccine. A literature review] | Frederiksen, Marianne Sjolin; Plesner, Anne-Marie; Stellfeld, Michael | 2003 | https://pubmed.ncbi.nlm.nih.gov/12840997/ | Not a systematic review |
| 79 | The impact of varicella vaccination on varicella-related hospitalization rates: global data review | Hirose, M.; Gilio, A. E.; Ferronato, A. E.; Ragazzi, S. L. B. | 2016 | 10.1016/j.rppede.2016.03.001 | Not a systematic review |
| 80 | A review of varicella vaccine and Louisiana vaccination requirements | Buff, Ann M.; Welch, Frank J.; Tapia, Ruben A. | 2004 | https://pubmed.ncbi.nlm.nih.gov/15000215/ | Not a systematic review |

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| 81 | JCVI Statement on varicella and herpes zoster vaccines - 29 March 2010 | JCVI | 2010 | https://webarchive.nationalarchives.gov.uk/ukgwa/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf | Not a systematic review |
| 82 | Prevention of Varicella | ACIP | 2007 | https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm | Not a systematic review |
| 83 | Impact of routine pediatric varicella vaccination on the epidemiology of herpes zoster | Alain, S.; Paccalin, M.; Larnaudie, S.; Perreaux, F.; Launay, O. | 2009 | 10.1016/j.medmal.2009.04.009 | Not a systematic review |
| 84 | Clinical trials of varicella vaccine in healthy children | White, C Jo | 1996 | 10.1016/S0891-5520(05)70315-9 | Not a systematic review |
| 85 | Primary versus secondary failure after varicella vaccination: Implications for interval between 2 doses | Bonanni, P.; Gershon, A.; Gershon, M.; Kulcsar, A.; Papaevangelou, V.; Rentier, B.; Sadzot-Delvaux, C.; Usonis, V.; Vesikari, T.; Weil-Olivier, C.; De Winter, P.; Wutzler, P. | 2013 | 10.1097/INF.0b013e31828b7def | Not a systematic review |
| 86 | Recommendations for immunization against varicella | Berthet F, Biver A | 2009 | https://sante.public.lu/dam-assets/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/varicelle/2009-vaccination.pdf | Not a systematic review |
| 87 | Vaccinating children, adolescents and at-risk individuals against varicella | Conseil Supérieur de la Santé, Belgium | 2017 | https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/css_avis_9212_varicelle_veerle_a5.pdf | Not a systematic review |
| 88 | Vaccinating children against varicella: are two doses of vaccine necessary? | Ucakar, Veronika; Socan, Maja | 2012 | 10.2478/v10152-012-0023-z | Not a systematic review |
| 89 | Vaccination against chicken pox. Up-date and new authorized indications in Spain | Barrio Corrales, F. | 2004 | https://www.seinap.es/wp-content/uploads/Revista-de-Pediatria/2004/REP%2060-4.pdf | Not a systematic review |

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| 90 | Varicella epidemiology in Latin America and the Caribbean | Ãvila-Aguero, M. L.; Beltran, S.; Castillo, J. B. D.; Castillo Diaz, M. E.; Chaparro, L. E.; Deseda, C.; Debbag, R.; Espinal, C.; Falleiros-Arlant, L. H.; Gonzalez Mata, A. J.; Macias Parra, M.; Marques-Rosa, F.; Catalina Pirez, M.; Vazquez-Rivera, M. | 2018 | 10.1080/14760584.2018.1418327 | Not a systematic review |
| 91 | Varicella-zoster virus: aspects of pathogenesis and host response to natural infection and varicella vaccine | Arvin, Ann M; Moffat, Jennifer F; Redman, Rebecca | 1996 | 10.1016/S0065-3527(08)60074-3 | Not a systematic review |
| 92 | Literature Review on One-Dose and Two-Dose Varicella Vaccination | Campbell, A; Ismail, S; Tan, B | 2010 | 10.14745/ccdr.v36i00a10 | Not a systematic review |
| 93 | Varicella prevention in the United States: A review of successes and challenges | Marin, M.; Meissner, H. C.; Seward, J. F. | 2008 | 10.1542/peds.2008-0567 | Not a systematic review |
| 94 | Varicella vaccine effectiveness in the US vaccination program: a review | Seward, J. F.; Marin, M.; Vazquez, M. | 2008 | 10.1086/522145 | Not a systematic review |
| 95 | Preventive effectiveness of varicella vaccine in healthy unexposed patients | Castro, Maria Catalina; Rojas, Pamela | 2020 | 10.5867/medwave.2020.06.7982 | Not a systematic review |
| 96 | [Varicella: clinical aspects and prevention] | Carvalho, E. S.; Martins, R. M. | 1999 | 10.2223/jped.379 | Not a systematic review |
| 97 | Chickenpox | Swingler, George H. | 2007 | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2943770/ | Not a systematic review |
| 98 | The state of vaccine safety science: systematic reviews of the evidence | Dudley, M. Z.; Halsey, N. A.; Omer, S. B.; Orenstein, W. A.; O'Leary, S. T.; Limaye, R. J.; Salmon, D. A. | 2020 | 10.1016/S1473-3099(20)30130-4 | Not a systematic review |
| 99 | NACI Varicella Vaccination Two-Dose Recommendations | NACI | 2010 | https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2010-36/canada-communicable-disease-report-1.html | Not a systematic review |
| 100 | Varicella vaccination two-dose recommendations. National Advisory Committee on Immunization (NACI) | Tan, B., Ismail, S. | 2010 | 10.14745/ccdr.v36i00a08 | Not a systematic review |

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| 101 | Varicella and herpes zoster vaccines | WHO | 2014 | https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/varicella/who-pp-varicella-herpes-zoster-june2014-references.pdf?sfvrsn=31c10d0a_2 | Not a systematic review |
| 102 | Modified chickenpox in children immunized with the Oka/Merck varicella vaccine | Watson, Barbara M; Piercy, Sharon A; Plotkin, Stanley A; Starr, Stuart E | 1993 | https://pubmed.ncbi.nlm.nih.gov/8416499/ | Not a systematic review |
| 103 | Keratitis in association with herpes zoster and varicella vaccines | Grillo, A. P.; Fraunfelder, F. W. | 2017 | 10.1358/dot.2017.53.7.2667582 | Not a systematic review |
| 104 | A new combination vaccine for measles, mumps, rubella and varicella | Zareba, G. | 2006 | 10.1358/dot.2006.42.5.973586 | Not a systematic review |
| 105 | Immunoprophylaxis of chickenpox and shingles | Petkova, T.; Doychinova, Tz | 2016 | https://www.researchgate.net/publication/316666392_Immunoprophylaxis_of_chickenpox_and_shingles | Not a systematic review |
| 106 | Safety of Vaccines Used for Routine Immunization in the United States | Maglione, Margaret A.; Gidengil, Courtney; Das, Lopamudra; Raaen, Laura; Smith, Alexandria; Chari, Ramya; Newberry, Sydney; Hempel, Susanne; Shanman, Roberta; Perry, Tanja; Goetz, Matthew Bidwell | 2014 | 10.23970/AHRQEPCERTA215 | Review has been updated |
| 107 | Safety of vaccines used for routine immunization of US children: A systematic review | Maglione, M.A; Das, L; Raaen, L; Smith, A; Chari, R; Newberry, S; Shanman, R; Perry, T; Goetz, M. B.; Gidengil, C. | 2014 | 10.1542/peds.2014-1079 | Review has been updated |
| 108 | Use of varicella vaccine in healthy populations: systematic review and recommendations | Skull, S. A.; Wang, E. E. L.; with the Canadian Task Force on Preventive Health, Care | 2000 | https://canadiantaskforce.ca/wp-content/uploads/2016/09/2001-varicella-vaccine-systematic-review-and-recommendations-en.pdf | Review has been updated |
| 109 | Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: a meta-analysis of randomized controlled trials | Leung, Julia Hy; Hirai, Hoyee W; Tsoi, Kelvin Kf | 2015 | 10.1586/14760584.2015.1057572 | Wrong comparator |
| 110 | Meta analysis on the safety and immunogenicity of domestic varicella vaccine among Chinese population. [Chinese] | Li, LanXin, He, Jia | 2013 | https://caod.oriprobe.com/articles/37711085/guo_chan_shui_dou_jian_du_huo_yi_miao_zai_zhong_gu.htm | Wrong comparator |

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| 111 | Immunogenicity and safety of measles-mumps-rubella-varicella vaccine: A systematic review | Wu, YM; Li, G; Zhao, WL | 2010 | http://caod.oriprobe.com/articles/24297599/Immunogenicity_and_Safety_of_Measles_Mumps_Rubella_Varicella_Vaccine__.htm | Wrong comparator |
| 112 | Safety of Vaccines Used for Routine Immunization in the United States: An Update | Gidengil, Courtney; Goetz, Matthew Bidwell; Maglione, Margaret; Newberry, Sydne J; Chen, Peggy; O'Hollaren, Kelsey; Qureshi, Nabeel; Scholl, Keller; Akinniranye, O; Kim, TM; Jimoh, O; Xenakis, L; Kong, W; Xu, Z; Hall, O; Larkin, J; Motala, A ; Hempel, S | 2021 | 10.23970/AHRQEPCCER244 | Wrong outcome |
| 113 | Safety of Co-administration versus separate administration of the same vaccines in children: A systematic literature review | Bauwens, J; Saenz, L. H; Reusser, A; Künzli, N; Bonhoeffer, J. | 2020 | 10.3390/vaccines8010012 | Wrong outcome |
| 114 | Combination Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children | Ma, S. J; Li, X; Xiong, Y. Q; Yao, A. L; Chen, Q. | 2015 | 10.1097/MD.0000000000001721 | Wrong outcome |
| 115 | Transmission of vaccine-strain varicella-zoster virus: A systematic review | Marin, M; Leung, J; Gershon, A. A. | 2019 | 10.1542/peds.2019-1305 | Wrong outcome |
| 116 | Is there an association between Stevens-Johnson Syndrome and vaccination? A systematic review | Grazina, I; Mannocci, A; Meggiolaro, A; La Torre, G. | 2020 | 10.7416/ai.2020.2333 | Wrong outcome |
| 117 | Primary varicella zoster infection compared to varicella vaccine reactivation associated meningitis in immunocompetent children | Amaral, Vanessa; Shi, Julia Zhuo; Tsang, Anita Man-Ching; Chiu, Susan Shui-Seng | 2021 | 10.1111/jpc.15303 | Wrong outcome |
| 118 | Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis | Ma, S. J; Xiong, Y. Q; Jiang, L. N; Chen, Q. | 2015 | 10.1016/j.vaccine.2015.06.009 | Wrong outcome |

## Appendix A5.1 Search strategies and grey literature searches

| **Database Name** | Embase (Elsevier) | |
|---|---|---|
| **Date search run** | 2 February 2022 | |
| **#** | **Search string** | **Number of results** |
| #1 | chickenpox:ab,ti OR 'chicken pox':ab,ti OR varicella:ab,ti OR 'varicella-zoster virus':ab,ti | 21,855 |
| #2 | 'chickenpox'/exp | 13,311 |
| #3 | #1 OR #2 | 25,964 |
| #4 | vaccin* OR immuni* OR inocula*:ab,ti | 1,277,298 |
| #5 | varilrix OR varivax OR 'priorix tetra' OR proquad OR mmrv:ab,ti | 1,091 |
| #6 | 'vaccination'/exp OR 'immunization'/exp OR 'chickenpox vaccine'/exp OR 'chickenpox measles mumps rubella vaccine'/exp | 338,787 |
| #7 | #4 OR #5 OR #6 | 1,285,095 |
| #8 | (systematic NEAR/2 (review* OR overview*)):ab,ti | 296,650 |
| #9 | (literature NEAR/3 (review* OR overview*)):ab,ti | 410,442 |
| #10 | 'meta analys*':ab,ti OR 'meta analyz*':ab,ti | 279,930 |
| #11 | 'systematic review'/exp OR 'meta analysis'/exp | 441,459 |
| #12 | #8 OR #9 OR #10 OR #11 | 886,109 |
| #13 | #3 AND #7 AND #12 | 393 |

| **Database Name** | Medline Complete (EBSCO) |
|---|---|
| **Date search run** | 2 February 2022 |

| # | Search string | Number of results |
|---|---|---|
| S1 | AB ( Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus" ) OR TI ( Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus" ) | 16,938 |
| S2 | (MH "Chickenpox") | 7,678 |
| S3 | S1 OR S2 | 18,110 |
| S4 | AB ( vaccin* OR immuni* OR inocula* ) OR TI ( vaccin* OR immuni* OR inocula* ) | 713,757 |
| S5 | (MH "Vaccination+") OR (MH "Immunization+") | 192,239 |
| S6 | (MH "Chickenpox Vaccine+") | 3,086 |
| S7 | AB ( varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV ) OR TI ( varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV ) | 300 |
| S8 | S4 OR S5 OR S6 OR S7 | 769,302 |
| S9 | MH "Systematic Review" OR MH "Meta Analysis" OR PT "Meta-Analysis" 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 N2 (review* OR overview*) | 674,058 |
| S10 | S3 AND S8 AND S9 | 201 |

| **Database Name** | The Cochrane Library | |
|---|---|---|
| **Date search run** | 2 February 2022 | |
| **#** | **Search string** | **Number of results** |
| #1 | (Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus"):ti,ab,kw (Word variations will be searched) | 959 |
| #2 | MeSH descriptor: [Chickenpox] explode all trees | 132 |
| #3 | #1 OR #2 | 959 |
| #4 | (vaccin* OR immuni* OR inocula*):ti,ab,kw (Word variations will be searched) | 36,681 |
| #5 | (varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV):ti,ab,kw (Word variations will be searched) | 170 |
| #6 | MeSH descriptor: [Immunization] explode all trees | 5,226 |
| #7 | MeSH descriptor: [Chickenpox Vaccine] explode all trees | 206 |
| #8 | MeSH descriptor: [Vaccination] explode all trees | 2,752 |
| #9 | #4 OR #5 OR #6 OR #7 OR #8 | 36,798 |
| #10 | #3 AND #9 in Cochrane Reviews, Cochrane Protocols | 6 |

| **Database Name** | Google Scholar |
|---|---|
| **Date search run** | 2 February 2022 |
| **Search string** | **Number of results** |
| (intext:varicella OR intitle:chickenpox) (intext:vaccine OR intext:vaccination OR intext:immunise OR intext:immunisation OR intext:immunize OR intext:immunization OR intext:inoculate OR intext:inoculation)<br><br>Searched first five pages (100 results) and selected the option: 'sort by relevance' and used the limiter: Any type 'Review'. | 100 |

| **Database Name** | TRIP database |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| (title:varicella OR title:chickenpox) (vaccin* OR inocula* OR immuni*)<br><br>Search limited to results filtered with the label:"systematic reviews" | 42 |

| **Database Name** | International HTA database |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| ("Chickenpox"[mh]) OR (varicella OR chickenpox)[Keywords] | 3 |

| **Database Name** | Domain specific and google non-domain specific searches (see list of domains in table below) |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| "(intext:varicella OR intext:chickenpox OR intext:'chicken pox' OR intext:'chicken-pox') (intext:vaccine OR intext:vaccination OR intext:immunise OR intext:immunisation OR intext:immunize OR intext:immunization OR intext:inoculate OR intext:inoculation) (intext:'systematic review' OR intext:meta-analysis OR intext:meta-analyses)"<br><br>Search limited to 1,000 hits per website and filetype 'pdf'. | 1,000 |

| **Database Name** | TRIP database |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |

| | |
|---|---|
| (title:varicella OR title:chickenpox) (vaccin* OR inocula* OR immuni*)<br><br>Search limited to results filtered with the label:"systematic reviews" | 42 |

| **Database Name** | SYSVAC registry |
|---|---|
| **Date search run** | 7 February 2022 |
| **Search string** | **Number of results** |
| Keyword search for "varicella" and "chickenpox" and combined results | 18 |

| **Database Name** | Prospero | |
|---|---|---|
| **Date search run** | 7 February 2022 | |
| **#** | **Search string** | **Number of results** |
| Multiple keyword searches (see #1 - #3) and a search for the MeSH term Chickenpox vaccine (#4). Results were scanned for relevant results. | | 10 |
| #1 | Varicella OR chickenpox | |
| #2 | Varicella vaccine* | |
| #3 | Chickenpox vaccine* | |
| #4 | MeSH DESCRIPTOR Chickenpox Vaccine EXPLODE ALL TREES | |

## Website domains for Heath Technology Assessment (HTA) agencies and Ministries of Health

| Country | Name of Agency/Unit/Ministry | Website domain |
|---|---|---|
| Norway | The National system for introduction of new methods in Specialist Health Care | nyemetoder.no |
| Norway | Norwegian Directorate of Health | helsedirektoratet.no |
| Norway | Norwegian Institute of Public Health (NIPHNO) | fhi.no |
| Norway | Norwegian Medicines Agency (NOMA) | legemiddelverket.no |
| Norway | Norwegian Centre for E-health Research | ehealthresearch.no |
| Norway | Ministry of Health and Care Services | regjeringen.no |
| Ireland | Health Information and Quality Authority (HIQA) | hiqa.ie |
| Ireland | National Centre for Pharmacoeconomics (NCPE) | ncpe.ie |
| Ireland | Department of Health | gov.ie |
| Switzerland | Federal Office of Public Health | bag.admin.ch |
| Switzerland | Swiss Network for HTA | snhta.ch |
| Switzerland | Federal Office of Public Health | bag.admin.ch |
| Hong Kong, China (SAR) | Department of Health | dh.gov.hk |
| Iceland | Ministry of Health | government.is |
| Germany | Federal Joint Committee (G-BA) | g-ba.de |
| Germany | Institute for Medical Documentation and Information (DIMDI) | dimdi.de |
| Germany | Institute for Quality and Efficiency in Health Care (IQWIG) | iqwig.de |
| Germany | Federal Ministry of Health | bundesgesundheitsministerium.de |
| Sweden | The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) | sbu.se |
| Sweden | Medical Products Agency (Läkemedelsverket) | lakemedelsverket.se |
| Sweden | Dental and Pharmaceutical Benefits Agency (TLV) | tlv.se |
| Sweden | Ministry of Health and Social Affairs | government.se |
| Sweden | Public Health Agency (Folkhälsomyndigheten) | government.se |
| Australia | Pharmaceutical Benefits Advisory Committee | pbs.gov.au |
| Australia | Medical Services Advisory Committee | msac.gov.au |
| Australia | Department of Health | health.gov.au |
| Australia | Adelaide Health Technology Assessment, Univeristy of Adelaide | health.adelaide.edu.au |
| Australia | Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) | surgeons.org |
| Australia | Medical Services Advisory Committee | msac.gov.au |
| Australia | Pharmaceutical Benefits Scheme (PBS) | pbs.gov.au |
| Australia | Department of Health | health.gov.au |
| Netherlands | National Health Care Institute/ Zorginstituut | zorginstituutnederland.nl |
| Netherlands | Erasmus University Rotterdam | eur.nl |
| Netherlands | Utrecht University | uu.nl |
| Netherlands | Radboud University Medical Centre | radboudumc.nl |
| Netherlands | Organisation for Health Research and Development (ZonMw) | zonmw.nl |
| Netherlands | Ministry of Health, Welfare and Sport | government.nl |
| Denmark | Danish Health and Medicines Authority | sst.dk |

| Country | Name of Agency / Unit / Ministry | Website domain |
|---|---|---|
| Denmark | Social & Health Services and Labour Market Corporate Quality (DEFACTUM) | defactum.net |
| Denmark | Ministry of Health (Sundhedsministeriet) | sum.dk |
| Finland | National Institute for Health and Welfare | thl.fi |
| Finland | Finnish Coordinating Center for Health Technology Assessment | fincchta.fi |
| Finland | Finnish Medicines Agency (FIMEA) | fimea.fi |
| Finland | Ministry of Health and Social Affairs | stm.fi |
| Singapore | Performance & Technology Assessment Division, Ministry of Health | moh.gov.sg |
| Singapore | Ministry of Health | moh.gov.sg |
| Singapore | Agency for Care Effectiveness | ace-hta.gov.sg |
| United Kingdom | National Institute for Health Research | nihr.ac.uk |
| United Kingdom | National Institute for Health Research Innovation Observatory | io.nihr.ac.uk |
| United Kingdom | National Institute for Health and Care Excellence | nice.org.uk |
| United Kingdom | All Wales Therapeutics and Toxicology Centre | awttc.org |
| United Kingdom | Healthcare Improvement Scotland | healthcareimprovementscotland.org |
| United Kingdom | Health Technology Wales | healthtechnology.wales |
| United Kingdom | Department of Health & Social Care England | gov.uk |
| United Kingdom | Department of Health Northern Ireland | health-ni.gov.uk |
| United Kingdom | Health & Social Care Scotland | gov.scot |
| United Kingdom | Public Health Wales | phw.nhs.wales |
| Belgium | Belgian Health Care Knowledge Centre (KCE) | kce.gov.be |
| Belgium | Scientific Institute for Public Health | sciensano.be |
| Belgium | Institut national d'assurance maladie-invalidité (INAMI) | inami.fgov.be |
| Belgium | Federal Public Service Health, Food Chain Safety and Environment | health.belgium.be |
| New Zealand | National Health Committee | health.govt.nz |
| New Zealand | PHARMAC | pharmac.gov.nz |
| New Zealand | Ministry of Health | health.govt.nz |
| Canada | Canadian Agency for Drugs and Technologies in Health (CADTH) | cadth.ca |
| Canada | Institute of Health Economics | ihe.ca |
| Canada | National Institute of Excellence in Health and Social Services (INESSS) | iness.qc.ca |
| Canada | Ontario Health Canada | ontariohealth.ca |
| Canada | Health Canada | canada.ca |
| United States | Agency for Healthcare Research and Quality (AHRQ) | ahrq.gov |
| United States | Blue Cross Blue Shield Association | bcbs.com |
| United States | Center for Medical Technology Policy | cmtpnet.org |
| United States | Institute for Clinical and Economic Review | icer.org |
| United States | Kaiser Permanente | kaiserpermanente.org |
| United States | Patient Centered Outcomes Research Institute (PCORI) | pcori.org |
| United States | US Department of Human and Health Services (HHS) | hhs.gov |

| Country | Name of Agency / Unit / Ministry | Website domain |
|---|---|---|
| Austria | National Public Health Institute/ Gesundheit Österreich GmbH | goeg.at |
| Austria | Federation of Social Insurances/ Dachverband der Sozialversicherungsträger | sozialversicherung.at |
| Austria | Austrian Institute for Health Technology Assessment (AIHTA) GmbH | aihta.at |
| Austria | University for Health Sciences, Medical Informatics and Technology Tirol (UMIT) | umit.at |
| Austria | Ministry of Social Affairs, Health, Care and Consumer Protection | sozialministerium.at |
| Israel | Ministry of Health | health.gov.il |
| Japan | Medical technology evaluation team | pmda.go.jp |
| Japan | Ministry of Health, Labour and Welfare | mhlw.go.jp |
| Liechtenstein | Ministry of Social Affairs and Culture | regierung.li |
| Slovenia | Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) | jazmp.si |
| Slovenia | Ministry of Health | mz.gov.si |
| Slovenia | National Institute of Public Health | nijz.si |
| Slovenia | Ministry of Health | mz.gov.si |
| Korea (Republic of) | National Evidence-based Healthcare Collaborating Agency (NECA) | neca.re.kr |
| Korea (Republic of) | Ministry of Health and Welfare | mohw.go.kr |
| Luxembourg | Ministry of Social Security | mss.gouvernement.lu |
| Luxembourg | Ministry of Health | msan.gouvernement.lu |
| Spain | Spanish Network of Agencies for Health Technology Assessment and Services of the National Health System | redets.sanidad.gob.es |
| Spain | Agency for Medicines and Medical Devices | aemps.gob.es |
| Spain | Health Technology Assessment Agency (AETS) Institute for Health “Carlos III” | isciii.es |
| Spain | Andalusian HTA Agency (AETSA) | aetsa.org |
| Spain | Agency for Health Quality and Assessment of Catalonia (AQuAS) | aquas.gencat.cat |
| Spain | Foundation of Professor Novoa Santos | hospitalcoruna.sergas.es |
| Spain | Galician Agency for HTA (AVALIA-T) | avalia-t.sergas.es |
| Spain | Health Knowledge Agency (ACIS) | acis.sergas.es |
| Spain | Basque Foundation for Health Innovation and Research (BIOEF) | bioef.org |
| Spain | Directorate General for Pharmacy and Health Care Products (DGFPS MSPSI) | sanidad.gob.es |
| Spain | Andalusian Public Foundation on Progress and Health (FPS) | juntadeandalucia.es |
| Spain | Canarian Health Research Foundation (FUNCANIS) | funcanis.org |
| Spain | Evaluation and Planning Unit – Directorate of the Canary Islands Health Service (SESCS) | sescs.es |
| Spain | Basque Office for Health Technology Assessment (OSTEBA) | euskadi.eus |
| Spain | Health Sciences Institute of Aragon | aragon.es |
| Spain | Ministry of Health | mscbs.gob.es |
| France | Higher Health Authority/ Haute Autorité de Santé (HAS) | has-sante.fr |

| Country | Name of Agency / Unit / Ministry | Website domain |
|---|---|---|
| France | Public Assistance - Paris Hospital | aphp.fr |
| France | Ministry of Solidarity and Health | solidarites-sante.gouv.fr |
| Czechia | State Institute for Drug Control (SUKL) | sukl.eu |
| Czechia | Ministry of Health | mzcr.cz |
| Czechia | Ministry of Health | mzcr.cz |
| Malta | Office of the Chief Medical Officer | ehealth.gov.mt |
| Malta | Ministry of Health | health.gov.mt |
| Malta | Directorate for Pharmaceutical Affairs | health.gov.mt |
| Estonia | Institute of Family Medicine and Public Health, University of Tartu | tervis.ut.ee |
| Estonia | Ministry of Social Affairs | sm.ee |
| Italy | National Agency for Regional Health Services (AGENAS) | agenas.gov.it |
| Italy | Italian Medicines Agency (AIFA) | aifa.gov.it |
| Italy | Integrated University Hospital Verona | ospedaleuniverona.it |
| Italy | Ministry of Health | salute.gov.it |
| Italy | Region Emilia Romana | regione.emilia-romagna.it |
| Italy | Catholic University of the Sacred Heart Rome | roma.unicatt.it |
| Italy | Technology Assessment Unit, Padua Hospital, Veneto Region | sanita.padova.it |
| Italy | Veneto Region | regione.veneto.it |
| Italy | Regional Health & Social Agency (ASSR), Emilia Romana | assr.regione.emilia-romagna.it |
| Italy | HTA Unit in A.Gemelli Teaching Hospital | policlinicogemelli.it |
| Italy | Ministry of Health | salute.gov.it |
| United Arab Emirates | Ministry of Health and Prevention | mohap.gov.ae |
| Greece | National and Kapodistrian University of Athens | phs.uoa.gr |
| Greece | National Evaluation Center of Quality and Technology in S.A.- EKAPTY | ekapty.gr |
| Greece | National Organization for Medicines | eof.gr |
| Greece | National Organisation for Healthcare Provision | eopyy.gov.gr |
| Greece | Institute of Pharmaceutical Research and Technology | ifet.gr |
| Greece | Onassis Cardiac Surgery Centre | onasseio.gr |
| Greece | Ministry of Health and Welfare | gov.gr |
| Cyprus | Pharmaceutical Services Ministry of Health | moh.gov.cy |
| Cyprus | Ministry of Health | moh.gov.cy |
| Lithuania | State Health Care Accreditation Agency under the Ministry of Health | vaspvt.gov.lt |
| Lithuania | Institute of Hygiene | hi.lt |
| Lithuania | State Medicines Control Agency | vvkt.lt |
| Lithuania | Ministry of Health | sam.lrv.lt |
| Poland | Agency For Health Technology Assessment and Tariff Systems (AOTMiT) | aotm.gov.pl |
| Poland | Ministry of Health | gov.pl |
| Andorra | Ministry of Health | salud.ad |
| Latvia | State Agency of Medicines | zva.gov.lv |
| Latvia | National Health Service | vmnvd.gov.lv |

| Country | Name of Agency / Unit / Ministry | Website domain |
|---|---|---|
| Portugal | INFARMED - National Authority of Medicines and Health Products | infarmed.pt |
| Portugal | Central Administration of the Health System (ACSS) | acss.min-saude.pt |
| Slovakia | Ministry of Health | health.gov.sk |
| Slovakia | Faculty of Pharmacy, Comenius University Bratislava | fpharm.uniba.sk |
| Hungary | National Institute of Pharmacy and Nutrition | ogyei.gov.hu |
| Hungary | Health Services Management Training Center (Semmelweis University) | semmelweis.hu |
| Saudi Arabia | Ministry of Health | moh.gov.sa |
| Bahrain | Ministry of Health | moh.gob.bh |
| Chile | Ministry of Health | minisal.cl |
| Croatia | Agency for Quality and Accreditation in Health and Social Welfare | aaz.hr |
| Croatia | Ministry of Health | miz.hr |
| Croatia | Health Insurance Fund (CHIF) | hzzo.hr |
| Croatia | Institute of Public Health | hzjz.hr |
| Croatia | Ministry of Health | miz.hr |
| Qatar | Ministry of Public Health | moph.gov.qa |
| Argentina | Institute for Clinical Effectiveness and Health Policy (IECS) | iecs.org.ar |
| Argentina | Ministry of Health | argentina.gob.ar |
| Brunei Darussalam | Ministry of Health | moh.gov.bn |
| Montenegro | Institute for Medicines and Medical Devices | calims.me |
| Montenegro | Ministry of Health | gov.me |
| Romania | National Agency for Medicines and Medical Devices | anm.ro |
| Romania | National Institute of Public Health | insp.gov.ro |
| Romania | National School of Public Health, Management and Professional Development | snspms.ro |
| Romania | Babes-Bolayi University, Cluj School of Public Health | publichealth.ro |
| Romania | Ministry of Health | ms.ro |
| Palau | Ministry of Health | palauhelath.org |
| International | International Centre for Community-Driven Research | cc-dr.org |
| International | World Health Organization | who.int |
| International | European Centre for Disease Prevention and Control | ecdc.europa.eu |
| International | Centers for Disease Control and Prevention | cdc.gov |

# Appendix A5.2 Data Extraction Tables

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Amaral<br><br>2021<br><br>10.1111/jpc.15303<br><br>Funding source: NR<br><br>From (start date not reported) to 1 June 2020 | Cases of varicella reactivation meningitis post varicella vaccination in immunocompetent children<br><br>Mean age (±SD) when first vaccinated = 1.4yrs (±0.7) | **At least one-dose monovalent or quadrivalent MMRV, One-dose (n=8 studies)**<br>**Two-dose (n=1)** | Total: 9 studies (study design not reported) | NA | Up to 10yrs in 1 study (two-dose schedule)<br><br>Mean interval between vaccination and reactivation (± SD) = 5.6yrs (± 2.9) | Safety - varicella reactivation meningitis | **Safety - varicella reactivation meningitis**<br>• 9 cases of varicella reactivation meningitis post varicella vaccination, in immunocompetent children reported<br>• Mean age (± SD) at presentation of VZV meningitis = 7yrs (±3.4)<br>• Of these 9 cases, clinical data were presented for 8. Clinical presentation, n/N (%):<br>o headache 8/8 (100)<br>o vomiting 4/8 (50)<br>o fever 6/8 (75)<br>o rash 8/8 (100)<br>o photophobia 2/8 (25)<br>• Meningism in neurological exam, n/N (%): 5/8 (63)<br>• Resolution data presented for all 9 cases:<br>o full recovery without neurological sequelae n/N (%) 9/9 (100%). | In immunocompetent children, meningitis caused by varicella zoster virus (VZV) reactivation can occur following either primary VZV infection or VZV vaccination, though it is rare. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

Key: SD – standard deviation; VZV-varicella zoster virus

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Bauwens<br><br>2019<br><br>10.3390/vaccines8010012<br><br>No external funding received<br><br>1999 to 28 January 2019 | Paediatric population under 18yrs of age<br><br>Canada (n=1 study);<br>Finland (n=1);<br>Germany (n=1);<br>Germany & Italy (n=1);<br>Italy (n=1);<br>Philippines (n=2);<br>USA (n=3); | **VAR+MMR+Hib-HepB co-administration** (Dosage NR) | Total: 1 study<br>RCT (n=1)<br>n=822 children aged 12-15mths | VAR+MMR+Hib-HepB separate administration | NR | Safety (rash and rhinorrhoea) | **Safety – rash and rhinorrhoea**<br>• Significantly less rash (RD: -5.8%, RR: 0.6) and less rhinorrhoea (RD: -6.1%, RR: 0.7) after co-administration compared to separate administration. | Overall, the evidence on the safety of vaccine co-administrations compared to separate vaccine administrations is inconclusive and there is a paucity of large post-licensure studies addressing this issue. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | **MMRV+PCV7 co-administration** (Dosage NR) | Total: 1 study<br>RCT (n=1)<br>n=1027 children aged 12-15mths | MMRV+PCV7 separate administration | NR | Safety (nasopharyngitis and insomnia) | **Safety – nasopharyngitis and insomnia**<br>• Significantly less nasopharyngitis (RD: -3.5%, RR: 0.6) and insomnia after co-administration compared to separate administration. | | |
| | | **MMR + VAR co-administration** (Dosage NR) | Total: 3 studies<br>RCT (n=3)<br>n=2,514 children aged 12-24mths | MMR + VAR separate administration | NR | Safety (adverse events) | **Safety – adverse events**<br>• No statistically significant difference in adverse events (not specified) between groups following immunisation. | | |
| | | **MMRV + DTaP + Hib-HepB co-administration** (Dosage NR) | Total: 1 study<br>RCT (n=1)<br>n=1,915 children aged 12-15mths | MMRV + DTaP + Hib-HepB separate administration | | | | | |
| | | **MMRV + DTaP-HepB-IPV/Hib co-administration** (Dosage NR) | Total: 2 studies<br>RCT (n=2)<br>n=1,414 children aged 12-23mths | MMRV + DTaP-HepB-IPV/Hib separate administration | | | | | |
| | | **MMRV or MMR + DTaP-IPV/Hib or DTaP-HepB-IPV/Hib co-administration** (Dosage NR) | Total: 1 study<br>Case control (n=1)<br>n=590 children aged 16-23mths | MMRV or MMR + DTaP-IPV/Hib or DTaP-HepB-IPV/Hib separate administration | | | | | |
| | | **MMRV + MenACWY co-administration** (Dosage NR) | Total: 1 study<br>RCT (n=1)<br>n=100 children aged 12-23mths | MMRV + MenACWY separate administration | | | | | |
| | | **MMRV + MenC co-administration** | Total: 1 study<br>RCT (n=1) | MMRV + MenC separate administration | | | | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | (Dosage NR) | n=716 children aged 13-15mths | | | | | | |

Key: DTaP – diphtheria, tetanus, pertussis; DTaP-IPV/Hib – diphtheria, tetanus, pertussis, inactivated poliovirus and haemophilus influenzae type b conjugate; DTaP-HepB-IPV/Hib – diphtheria, tetanus pertussis, hepatitis B, inactivated poliovirus and haemophilus influenzae type b conjugate; Hib-HepB – haemophilus influenzae type b conjugate, hepatitis B; MenACWY - quadrivalent meningococcal conjugate; MenC – meningococcal Group C; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; NR – not reported; PCV7 – penumococcal conjugate 7-valent; RD – risk difference; RR – relative risk; VAR – varicella;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Benchimol<br><br>2021<br><br>10.1093/jcag/gwab015 and 10.1053/j.gastro.2020.12.079<br><br>Guideline was funded by the Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes, and CANImmunize.<br><br>Lead author supported by a New Investigator Award from the Canadian Institutes of Health Research, Crohn's and Colitis Canada, and CAG. He was also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program.<br><br>1989 to | Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy with the associated systematic review based on the general population (see below)<br><br>(While this paper relates to the development of immunisation guidelines for persons with inflammatory bowel disease, a systematic search for systematic reviews and meta analyses assessing the efficacy, effectiveness and safety of vaccines in the general population was also conducted). | **At least one-dose**<br>(vaccine type not reported) | Total: 2 studies<br>Systematic reviews (SR): n=2<br>(1 SR includes a further 2 SRs)<br><br>Safety outcome:<br>7 RCTs and 5 observational studies | No vaccination | NR | Safety of varicella vaccine (serious adverse events) | **Safety (serious adverse events)**<br>Few reports and low incidence of serious adverse events in RCTs, observational studies and post-marketing surveillance data. | Maintaining appropriate vaccination status in patients with IBD is critical to optimise patient outcomes. In general, live vaccines are recommended in patients not on immunosuppressive therapy, but not for those using immunosuppressive medications. | **Risk of bias**<br>Cochrane RoB for RCTs and ROBINS-I for non-randomised studies<br>Assessment for individual studies not provided.<br>Overall deemed 'not serious' for safety studies relating to serious adverse events in healthy children in the general population.<br><br>**Overall quality of evidence assessment**<br>Safety<br>The CoE of evidence for safety was anchored to the general population (healthy children), adapted from WHO Evidence Tables, and started as **MODERATE**. When the evidence was applied to paediatric IBD patients not on immunosuppressive medications, the evidence was not downgraded for indirectness. |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| 12 April 2019 | | | | | | | | | |

Key: CI – confidence interval; CoE – certainty of evidence; IBD – inflammatory bowel disease; RCT – randomised controlled trial; SR – systematic review; VE – vaccine effectiveness; VZV – varicella zoster virus;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Di Pietrantonj<br><br>2021<br><br>10.1002/14651858.CD004407.pub5<br><br>National Institute for Health Research (NIHR) via the NIHR Cochrane Incentive Award Scheme 2018 - 128383<br><br>Medline from 1966 and Embase from 1974 to 2 May 2019 | n=181,088 children aged up to 15yrs | **Monovalent MMR+V** | Total: 1 study<br>**Self-controlled case series/ person time cohort** (n=1) | Unvaccinated | 1-2 weeks after vaccination | Safety: Seizures (febrile/afebrile) | **Pooled rate ratio (rr) for seizures (95% CI)**<br>(random effects model)<br>• Overall (n=2 estimates): 3.13 (2.38 to 4.10, $I^2$=0%) | Our review shows that MMRV and MMR+V vaccines are effective in preventing the infection of children by chickenpox with no evidence of an increased risk of autism or encephalitis and a small risk of febrile seizure. | **Risk of bias**<br>Risk of bias conducted for all primary studies.<br><br>Case-control (prospective and retrospective) and cohort studies assessed using the appropriate Newcastle-Ottawa Scales.<br><br>Case-only ecological method studies, self-controlled case series and person time cohort studies assessed for *case selection, exposure, observation and exposure risk* |
| | n=180,480 children aged up to 15yrs | **Quadrivalent MMRV** | Total: 2 studies<br>**Self-controlled case series/ person time cohort** (n=2) | | | | **Pooled rr for seizures (95% CI)**<br>(random effects model)<br>• Overall (n=4 estimates): 6.08 (4.95 to 7.47, $I^2$=0%) | | |
| | n=1,342,366 children aged up to 15yrs | **Quadrivalent MMRV**<br>Priorix-Tetra and ProQuad | Total: 5 studies<br>**Cohort study** (n=5) | MMR (no varicella vaccine) | 0-42 days after vaccination | Safety: Seizures (febrile/afebrile) | **Pooled RR for seizures (95% CI)**<br>(fixed effects model)<br>• Overall (n=6 estimates): 1.53 (1.37 to 1.71, $I^2$=71%)<br>• Priorix-Tetra (n=3 estimates from 2 studies): 1.28 (1.00 to 1.64, $I^2$=0%)<br>• ProQuad (n=3 estimates from 3 studies): 1.60 (1.42 to 1.82, $I^2$=85%) | | |
| | n=2,281,652 children aged up to 15yrs | **Quadrivalent MMRV**<br>Priorix-Tetra and ProQuad | Total: 6 studies<br>**Cohort study** (n=6) | MMR (no varicella vaccine) | 7-10 days after vaccination | Safety: Seizures (febrile/afebrile) | **Pooled RR for seizures (95% CI)**<br>(fixed effects model)<br>• Overall (n=7 estimates): 1.50 (1.36 to 1.66, $I^2$=81%)<br>• Priorix-Tetra (n=3 estimates from 2 studies): 2.49 (1.66 to 3.74, $I^2$=0%)<br>• ProQuad (n=4 estimates from 4 studies): 1.46 (1.32 to 1.61, $I^2$=88%) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | Children aged 9-23mths aged up to 15yrs | **Quadrivalent MMRV** | Total: 1 study **Self-controlled case series** (n=1) | Unvaccinated | 7-10 days after vaccination | Safety: Idiopathic thrombocytopenic purpura | **rr for idiopathic thrombocytopenic purpura (95% CI)**<br>• Overall (n=1 estimate): 2.87 (0.78 to 10.56) | | *period and comparability*.<br><br>Safety studies 9/9 (100%) varicella studies rated as 'low' risk of bias.<br><br>**Overall quality of evidence assessment** GRADE Quality of Evidence assessment applied for **observational studies** examining risk of seizures (febrile/ afebrile) with MMRV and MMR+V vaccines. Certainty of evidence rated as LOW. |

Key: CI – confidence interval; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; NR – not reported; rr – rate ratio; RR – risk ratio; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Garrido<br><br>2012<br><br>10.32385/rpmgf.v28i2.10928<br><br>No funding received<br><br>January 2005 to November 2009 | Healthy children aged 1-12yrs at vaccination<br><br>Sample sizes varied across included studies (449 to 135,311) but were not reported for all studies | **One-dose**<br>(vaccine type not reported) | Total: 11 studies<br>Systematic reviews (SRs) (n=3);<br>Meta-analysis (n=1);<br>Primary studies (n=7) | No vaccination or placebo | NR | Safety (serious adverse events)<br><br>Safety (short term effects of vaccination) | **Vaccine safety**<br>• A SR analysing 41 (mostly observational) studies published in the USA reported that the vaccine has an excellent safety profile with infrequent serious adverse events (5% of notifications) and the most frequent adverse events (2/3rds of reports) were rash, fever and local reaction.<br>• A SR analysing 1 SR and an additional RCT reported the existence of larger maculopapular lesions in the vaccine group, although this difference was not statistically significant. No adverse events were reported in the RCT. | Considering the available evidence, it can be concluded that the varicella vaccine is an effective intervention and safe in healthy children. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>The Strength of Recommendation Taxonomy (SORT) scale from the American Family Physician Foundation was used.<br><br>3 of the 4 SRs/meta-analysis and 1 of the 7 primary studies were graded as Level 1 evidence (good quality patient orientated evidence). The remaining studies were not graded. |
| | | **At least one dose**<br>(vaccine type not reported) | | No vaccination | | Safety (short term effects of vaccination)<br><br>Safety (adverse events)<br><br>Safety (death) | **Vaccine safety**<br>• An observational study reported that varicella cases in the unvaccinated are more severe (increased likelihood of generalised rash, fever and other symptoms) with a longer rash duration compared to those vaccinated. 2 cases of complications were recorded: conjunctivitis in an unvaccinated child and bacterial infection of the skin in a vaccinated child.<br>• An observational study (1995 to 2005) in the USA reported that the most frequent adverse events associated with the vaccine were rash, fever, injection site reaction and urticaria, with the majority | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | occurring in children aged 12-23mths who had received the vaccine at the same time as other vaccines. Of the 25,306 adverse events (52.7/100,000 of the distributed cases), 5% were classified as serious events (herpes zoster ophthalmicus, pneumonia, encephalitis, thrombocytopenia, vasculitis and hepatitis), with most occurring in children with previous co-morbidity. The rate of serious adverse events declined over the 10yrs of the study. Some deaths have been reported after vaccination, however a consistent association has not been proven. The study concluded that the vaccine has an excellent safety profile, with rare serious adverse effects, so the benefits conferred outweigh the potential risks.<br>• An RCT in France and Italy reported that among 507 children vaccinated for varicella, 47.7% had at least one adverse effect related to the vaccine. 17.2% had a reaction at the injection site. Most of the reactions were minor/medium intensity. Systemic adverse events (65.1% of adverse effects) were mostly unrelated to the vaccine. Fever was the most frequent systemic adverse event (25.3%) with a verified relationship with the vaccine. Four serious adverse events were reported: idiopathic cytopenic thrombus purpura, gastroenteritis, pneumonia and laryngospasm. The study | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | concluded that the vaccine is safe and has a good tolerability profile in children aged 12-15mths. | | |

Key: BV – breakthrough varicella; RCT – randomised controlled trial; SR – systematic review; USA – United States of America; UVV- universal varicella vaccination; VE – vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Gidengil (Agency for Healthcare Research and Quality - AHRQ)<br><br>2021<br>(this is an update of 2014 AHRQ report, which itself built upon the 2011 Institute of Medicine (IOM) consensus report)‡<br><br>10.23970/AHRQEPCCER244<br><br>10.1016/j.vaccine.2021.03.079 (linked publication)<br><br>Funded under Contract No. HHSA290201600010I from the AHRQ, U.S. Department of Health and Human Services (HHS).<br><br>At least 2011 to November 2020<br><br>‡ 'Summary of main findings' | Children (11-23mths) for whom vaccines for routine immunisation in the United States are recommended | **Monovalent Varivax and unspecified brand**<br>(Dosage NR) | n=4 studies on monovalent varicella vaccine identified for 2021 update<br><br>Study type:<br>Cohort (n=1);<br>Case-control (n=1);<br>Self-controlled risk interval analysis (n=1);<br>Other (n=2) | Active and inactive comparators<br><br>Age at vaccination (seizures) | Various – including up to 9mths | Safety – various outcomes including analphylaxis, disseminated Oka VZV, vaccine strain viral reactivation, acute disseminated encephalomyelitis, febrile seizures, optic neuritis, seizures, sudden sensorineural hearing loss, transverse myelitis | **Summary - 2014 AHRQ Vaccine Safety Report**<br>• Causal relationship between varicella vaccine and:<br>o anaphylaxis<br>o disseminated Oka strain of VZV without other organ involvement (not examined as key adverse events in current report)<br>o vaccine strain viral reactivation without other organ involvement (herpes zoster)<br>o vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis,<br>all based on mechanistic evidence: HIGH Strength of Evidence (SoE)<br><br>**Findings in 2021 update**<br>• Insufficient evidence for the following outcomes:<br>o acute disseminated encephalomyelitis (1 study of children and adults reported no systematic increased risk [aOR 4.3; 95% CI 0.5, 25.4]<br>o febrile seizures (1 study reported no increased risk in the 0-1 days following VAR compared to a control period of 14-20 days [IRR 0.80; 95% CI 0.45, 1.42]. The risk interval may have been too short to detect a risk)<br>o optic neuritis (1 study of children and adults detected no systematic increased risk | Overall, our evidence review found vaccines to be safe across populations with serious adverse events being rare. Among children, there continues to be a reasonably robust body of evidence related to vaccine safety. | **Risk of bias**<br>Conducted using the McHarm Quality Assessment Scale for adverse events<br><br>**Overall quality of evidence assessment**<br>The body of evidence was assessed based on AHRQ Evidence-based Practice Center grading using the following four criteria to grade the SoE: (i) study limitations, (ii) consistency, (iii) precision and (iv) reporting bias.<br>See results in Summary of main findings. |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| over includes summary from 2014 AHRQ report, new studies identified since 2014 and summary from 2021 AHRQ report. | | | | | | | [aOR 2.1; 95% CI 0.1 to 23.2])<br>o seizures (1 self-controlled risk interval analysis reported no increased risk of seizures [IRR 0.8; 95% CI 0.6 to 1.0]. The same study reported the risk of seizures with varicella vaccine given concomitantly with other vaccines, including MMR, found that the risk 7-10 days after vaccination increased with age, from an IRR of 2.75 [95% CI 2.05 to 3.70) at age 12 to 15 mths to 3.64 (95% CI 1.86 to 7.12) when administered at 16 to 23 mths of age).<br>o sudden sensorineural hearing loss (1 study reported no association within 1 week of vaccination)<br>o transverse myelitis (1 study of children and adults reported no increased risk [aOR 0; 95% CI 0.00 to 10.7])<br>o others (1 study in children aged 6 to 15yrs reported no association with a diagnosis of broken bone, open wound, obsessive-compulsive disorder, anorexia, tic disorder, attention deficit hyperactive disorder, major depression, or bipolar disorder).<br><br>• No studies identified reporting on the following outcomes:<br>o anaphylaxis or systemic allergic reaction<br>o angioedema<br>o ataxia<br>o cardiovascular events<br>o death | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | o diabetes<br>o encephalitis/encephalopathy<br>o Guillain-Barré syndrome<br>o herpes zoster<br>o idiopathic thrombocytopenic purpura<br>o meningitis<br>o secondary transmission of live varicella virus<br>o stroke.<br><br>**Summary - 2021 AHRQ Vaccine Safety Report**<br>(no change from 2014 Report)<br>• High Strength of Evidence (SoE) of increased risk of the following adverse events (causal relationship based on mechanistic evidence):<br>o anapyhlaxis<br>o disseminated Oka VZV without other organ involvement<br>o vaccine strain viral reactivation without other organ involvement (herpes zoster)<br>o vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis.<br>Estimates of the magnitude of increased risk was not determined.<br><br>• Insufficient SoE of increased risk of the following adverse events:<br>o seizures<br>o acute disseminated encephalomyelitis<br>o transverse myelitis<br>o Guillain-Barré syndrome<br>o small fibre neuropathy<br>o onset or exacerbation of arthropathy and thrombocytopenia | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | as new evidence was either graded as insufficient, there were no studies, or the outcome was not included as a key adverse event. | | |
| | | **Quadrivalent MMRV (ProQuad)** (Dosage unclear) | Total: n=5/6 studies identified on quadrivalent MMRV vaccine for 2021 update<br><br>Study type:<br>RCT (n=1);<br>Cohort (n=2);<br>Self-controlled risk interval analysis (n=1)<br>Other (n=2) | Active and inactive comparators<br><br>Concomitant administration with another vaccine (febrile seizures)<br><br>Age at vaccination (seizures) | Unclear | Safety – various outcomes including encephalitis/ encephalopathy, death, anayphylaxis, ataxia, febrile seizures, idiopathic thrombocytopenic purpura, Kawasaki disease, meningitis, seizures | **Summary - 2014 AHRQ Vaccine Safety Report**<br>• No findings<br><br>**Findings in 2021 update**<br>• Low SoE for no increased risk for the following outcomes:<br>o acute disseminated encephalomyelitis (2 cohort studies [1 in children and adults] reported no increased risk [no estimable risk for first study; aOR 0; 95% CI 0.0 to 292.0 in 2nd study involving 9-26yr olds]).<br>o death (1 RCT; RR 0.50; 95% CI 0.01 to 25.33 [Number of events: 0/474 vs 0/239]).<br><br>• Insufficient evidence for the following outcomes:<br>o anaphylaxis or systemic allergic reaction (1 cohort study reported an increased risk [RR 15.34; 95% CI 2.16 to 108.86] but on chart review, both cases were noted not to be anaphylaxis.<br>o ataxia (1 cohort study reported no increased risk)<br>o febrile seizures (1 RCT comparing MMRV with a hexavalent vaccine to hexavalent vaccine alone identified 2 participants with febrile seizures in the intervention arm compared to none in the control arm. Both had concomitant infections and the difference was not statistically significant [RR 2.02; 95% CI | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0.09 to 44.55]. 1 study reported no increased risk of febrile seizures in the 0-1 days following MMRV compared to a control period of 14-20 days [IRR 1.12; 95% CI 0.49 to 2.54]. The risk interval may have been too short to detect a risk).<br>o idiopathic thrombocytopenic purpura (1 cohort study reported an increased risk for some time intervals [RR 11.28; 95% CI 1.87 to 68.2]).<br>o Kawasaki disease (1 cohort study reported no increased risk)<br>o meningitis (1 cohort study reported no increased risk of meningitis/encephalitis (combined outcome)<br>o seizures and fever (2 studies reported an increased risk of seizures: - a self-controlled risk interval analysis comparing the risk during the 7-10 days following MMRV vaccination to a control window of 15 to 42 days found significantly increased risk of seizures both in children who had been born full-term [IRR 5.7 95% CI 4.1 to 7.8] and pre-term [IRR 7.9 95% CI 3.0 to 20]. A second cohort study compared risk of seizures following MMRV in a number of ways, including through unadjusted risk differences, case-centered analysis comparing MMRV to itself. All analyses showed an increased risk of seizures, with an adjusted RR of 1.99 [95% CI 1.08 to 3.52] | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | among children, as well as risk of fever. The authors of both of the studies of MMRV and seizures note that based on prior analyses, the majority of seizures were presumed to be febrile seizures.<br>o seizures - risk factors (a study that assessed the risk of seizures with varicella vaccine given concomitantly with other vaccines reported that MMRV was associated with an increased risk of seizures by age at vaccination [IRR 4.95; 95% CI 3.68 to 6.66 at 12-15 months vs IRR 9.80; 95% CI 4.35 to 22.06 at 16-23 months]. A second study of measles containing vaccines, including MMRV, found lower increased risk of seizures when the vaccine was administered at 12-15mths of age compared to 16-23mths of age. A further study examining the risk of seizures with MMRV found no significant difference in the risk for children who had been born pre-term compared to full-term [IRR 1.4; 95% CI 0.51 to 3.8]).<br><br>• No studies identified reporting on the following outcomes:<br>o angioedema<br>o autism<br>o cardiovascular events<br>o diabetes<br>o encephalitis/encephalopathy<br>o Guillain-Barré syndrome<br>o herpes zoster<br>o multiple sclerosis | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | o secondary transmission of live varicella virus<br>o stroke<br>o transverse myelitis.<br><br>**Summary - 2021 AHRQ Vaccine Safety Report**<br>• LOW SoE of increased risk of the following outcomes:<br>o acute disseminated encephalomyelitis<br>o death. | | |

Key: aOR – adjusted odds ratio; CI – confidence interval; IRR – incidence risk ratio; RR – relative risk; SoE – Strength of Evidence; VZV – varicella zoster virus;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Grazina<br><br>2020<br><br>10.7416/ai.2020.2333<br><br>Not funded<br><br>1 January 2000 - February 2018 | Vaccinated individuals who developed Stevens-Johnson Syndrome (SJS)<br><br>Included study: 27mth old baby | **Varicella vaccine** | Total: 1 study<br>Case report and review (n=1)) | NA | NR | Safety: Development of Stevens-Johnson Syndrome after vaccination | **Safety - Stevens-Johnson Syndrome**<br>• 1 case of SJS following the administration of varicella vaccine, in a 27mth old baby (not reported whether the infant was immunocompetent or not).<br>• In the same study, the authors reviewed the data from the vaccine adverse event reporting system, where 1 definite case of SJS/toxic epidermal necrolysis (TEN) and 5 probable cases were diagnosed, after vaccination.<br>• A causal link between vaccination and SJS cannot be established by this study. | In this review it was not possible to establish a positive relationship between vaccination and the development of SJS. | **Risk of bias**<br>Conducted as per a case report conceptual scheme. Single included varicella study rated 3 out of a maximum of 10. Reports scoring ≤5 points are of great concern with respect to the 5 domains assessed and should not be published.<br><br>**Overall quality of evidence assessment**<br>Not conducted |

Key: NA – not applicable; NR – not reported; SJS – Stevens-Johnson syndrome; TEN - Toxic Epidermal Necrolysis

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Ma<br><br>2015_a<br><br>10.1097/MD.0000000000001721<br><br>No funding received<br><br>Earliest date available to 9 September 2014 | Healthy children aged 0 to 6yrs | **1-dose quadrivalent MMRV Priorix-Tetra (GSK)** | Total: 6 studies<br>RCT (n=6) | MMR | Within 4 days (0-3 days) after vaccination | Safety - solicited local symptoms: pain, redness and swelling | **Safety (pain, redness, swelling)**<br>• No significant differences were observed between MMRV and MMR groups in incidences of pain, redness, swelling, and their grade 3 levels after the single dose. Pooled Relative Risk (RR) (95% CI, $I^2$) (fixed effects model):<br>o Pain (any): RR 1.12 (0.95 to 1.32, $I^2$=0%)<br>o Pain (Grade 3): RR 0.94 (0.21 to 4.13, $I^2$=0%)<br>o Redness (any): RR 1.08 (0.96 to 1.22, $I^2$=24%)<br>o Redness (Grade 3): RR 1.18 (0.50 to 2.79, $I^2$=0%)<br>o Swelling (any): RR 1.22 (0.96 to 1.55, $I^2$=0%)<br>o Swelling (Grade 3): RR 5.89 (0.72 to 48.16, $I^2$=0%)<br>• Redness most frequently reported, 18.45% for MMRV group and 16.21% for MMR group.<br>• Incidences of pain and swelling were around and below 10% in both groups, respectively.<br>• Grade 3 local reactions were rare (<0.5%) for both groups, especially pain. | This systematic review and meta-analysis showed rigorous evidence that MMRV had comparable overall safety profiles to MMR administered with or without varicella vaccine. | **Risk of bias**<br>Conducted using Jadad scale scoring from 0 (very poor quality) to 5 (rigorous).<br>8 RCTs scored 2; 2 RCTs scored 3<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | | Total: 5 studies<br>RCT (n=5) | | Within 43 days (0-42 days) after vaccination | Safety - solicited general symptoms: fever | **Safety (fever)**<br>• Fever was the most frequently reported solicited general symptom, pooled incidences of fever were around 60% in MMRV groups and 50% in MMR groups. Majority were reported during the first 15 days (days 0–14) follow-up | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | period. Pooled incidence rates of 2.82% and 1.37% for the MMRV and MMR groups respectively. Half of the events were considered by the investigator to be related to investigational vaccine.<br>• Pooled incidence of grade >39.5°C) 3 fever (rectal temperature during the 43 days after vaccination) in these studies was relatively low (around 15% in MMRV groups, 11% in MMR group).<br>• Irrespective of follow-up period (0-15 days or 0-42 days), significantly higher incidences of fever were reported in MMRV group than in MMR group (pooled RRs ranged from 1.19 to 1.60). | | |
| | | | Total: 3 studies RCT (n=3) | | Within 43 days (0-42 days) after vaccination | Safety - solicited general symptoms: rash | **Safety (rash)**<br>• Both incidences of measles/rubella-like rash and varicella-like rash were significantly higher in MMRV groups than those in MMR groups. Pooled RR (95% CI, $I^2$) (fixed effects model:<br>o RR measles/rubella-like rash: 1.45 (1.06 to 1.98, $I^2$=0%, p=0.020)<br>o RR varicella-like rash: 1.95 (1.04 to 3.66, $I^2$=0%, p=0.040). | | |
| | | | Total: 3 studies RCT (n=3) | | Within 43 days (0-42 days) after vaccination | Safety - unsolicited adverse events | **Safety (unsolicited adverse events)**<br>• 15 unsolicited adverse events (whether or not considered related to the vaccination studied) were analysed.<br>• Incidence of pharyngitis was statistically higher in MMRV group compared to the MMR group. Pooled RR (95% CI, $I^2$) (fixed effects model: | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
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| | | | | | | | o RR 1.37 (1.09 to 1.72, $I^{2}$ = 31%; p=0.008). | | |
| | | | Total: 5 studies RCT (n=5) | | Within 43 days (0-42 days) after vaccination | Safety – serious adverse events (SAE) | **Safety (SAEs)**<br>• Incidences of any SAEs (n=2 studies) were approximately 1% in both MMRV and MMR groups; 1/10 of SAEs were considered to be related to vaccination studied.<br>• Approximately 50% of the related SAEs (n=2 studies) were febrile seizures.<br>• The incidence of related febrile seizure was <0.8% in MMRV groups and <0.5% in MMR groups. No statistical difference was found between groups, with no evidence of heterogeneity.<br>• No related fatal SAE was reported in any studies included. | | |
| | | **Two-dose quadrivalent MMRV Priorix-Tetra (GSK) at interval of 4 wks to 6mths** | Total: 7 studies RCT (n=7) | One-dose MMRV | NR | Safety - solicited local symptoms: pain, redness, swelling | **Safety (pain, redness, swelling)**<br>• Although 1 or 2 solicited local symptoms (pain, redness, and swelling) were more frequently reported after the 2nd dose of MMRV compared to the 1st in most studies, incidences of most adverse experiences after the 2nd dose were similar among groups. | | |
| | | **2nd dose quadrivalent MMRV** | Total: 5 studies RCT (n=5) | NA | NA | Safety - tolerance | **Safety (tolerance)**<br>• MMRV was well tolerated when given as a second dose after MMR (3 studies) or MMR+V (2 studies) vaccination in children aged 15mths to 6yrs. | | |

Key: MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; MMR+V – measles, mumps, rubella vaccine and varicella vaccine administered concomitantly; NR – not reported; RCT – randomised controlled trial;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Ma<br><br>2015b<br><br>10.1016/j.vaccine.2015.06.009<br><br>Not funded<br><br>From earliest date available to 12 December 2014. | Searched for studies in all children aged 0-6 yrs – retrieved studies in healthy children aged 9-24 mths. | **First dose quadrivalent MMRV** (Brand not specified) | Total: 4 studies<br>RCT (n=4) | MMR | 0-42 days | Safety - febrile seizures | **Febrile seizures**<br>• Pooled incidence:<br>o MMRV: 1.95% (5/2566)<br>o MMR: 1.81% (2/1104)<br>• Pooled Risk Difference:<br>-0.40 (95% CI: -4.20 to 3.40)<br>• Pooled Risk Ratio:<br>0.71 (95% CI: 0.19 to 2.74) | Clinical studies did not find any difference in the incidence of febrile seizure or vaccine related febrile seizure between MMRV vaccine recipients and MMR and MMRV + others vaccine recipients after any doses.<br><br>However, an approximately 2-fold increase in risk for seizure or febrile seizure during 7-10 days or 5-12 days after MMRV vaccination among children aged 10-24mths was demonstrated in several post-marketing surveillance | **Risk of bias**<br>The quality of included clinical trials was assessed using the Jadad score (0 - poor and 5 – rigorous). Jadad scores were equivalent to 2 or 3 in all the clinical trials (out of a maximum of 5).<br><br>The quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS). All cohort studies included had at least 8 stars (out of a maximum of 9) using NOS.<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | | Total: 2 studies<br>RCT (n=2) | | 7-10 days | | **Febrile seizures**<br>• Pooled incidence:<br>o MMRV: 0% (0/542)<br>o MMR: 0% (0/275)<br>• Pooled Risk Difference:<br>0 (95% CI: -7.98 to 7.98)<br>• Pooled Risk Ratio:<br>0.51 (95% CI: 0.03 to 8.08) | | |
| | | | Total: 5 studies<br>RCT (n=5) | | 0-42 days | Safety - vaccine-related febrile seizures | **Vaccine-related febrile seizures**<br>• Pooled incidence:<br>o MMRV: 0.59% (3/5055)<br>o MMR: 0.22% (1/4598)<br>• Pooled Risk Difference:<br>0.58 (95% CI: -0.78 to 1.94)<br>• Pooled Risk Ratio:<br>1.39 (95% CI: 0.39 to 4.98) | | |
| | | | Total: 5 studies<br>RCT (n=5) | | 7-10 days | | **Vaccine-related febrile seizures**<br>• Pooled incidence:<br>o MMRV: 0.59% (3/5055)<br>o MMR: 0.22% (1/4598)<br>• Pooled Risk Difference:<br>0.58 (95% CI: -0.78 to 1.94)<br>• Pooled Risk Ratio:<br>1.39 (95% CI: 0.39 to 4.98) | | |
| | | **First dose quadrivalent MMRV plus other vaccines** (Brand not specified) | Total: 5 studies<br>RCT (n=5) | Other vaccines | 0–28/42 days | Safety - febrile seizures | **Febrile seizures**<br>• Pooled incidence:<br>o MMRV + others: 1.59% (3/1886)<br>o Others: 0% (0/2745) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • Pooled Risk Difference: 1.70 (95% CI: -1.43 to 4.82)<br>• Pooled Risk Ratio 2.52 (95% CI: 0.63 to 10.11) | studies. More post-marketing studies based on rigorously prospective study design are needed to confirm the findings. | |
| | | | Total: 5 studies<br>RCT (n=5) | | 7-10 days | | **Febrile seizures**<br>• Pooled incidence:<br>o MMRV + others: 0.53% (1/1886)<br>o Others: 0% (0/2745)<br>• Pooled Risk Difference: 0.35 (95% CI: -2.12 to 2.81)<br>• Pooled Risk Ratio: 1.41 (95% CI: 0.28 to 7.19) | | |
| | | | Total: 6 studies<br>RCT (n=6) | | 0–28/42 days | Safety - vaccine-related febrile seizures | **Vaccine-related febrile seizures**<br>• Pooled incidence:<br>o MMRV + others: 0.38% (1/2651)<br>o Others: 0% (0/3534)<br>• Pooled Risk Difference: 0.37 (95% CI: -1.61 to 2.35)<br>• Pooled Risk Ratio: 1.46 (95% CI: 0.34 to 6.25) | | |
| | | | Total: 6 studies<br>RCT (n=6) | | 7-10 days | | **Vaccine-related febrile seizures**<br>• Pooled incidence:<br>o MMRV + others: 0.38% (1/2651)<br>o Others: 0% (0/3534)<br>• Pooled Risk Difference: 0.37 (95% CI: -1.61 to 2.35)<br>• Pooled Risk Ratio: 1.46 (95% CI: 0.34 to 6.25) | | |
| | | **Second dose quadrivalent MMRV** (Brand not specified) | Total: 2 studies<br>RCT (n=2) | MMR | 0-42 days | Safety - febrile seizures | **Febrile seizures**<br>• Pooled incidence:<br>o MMRV: 1.43% (1/700)<br>o MMR: 3.28% (1/305)<br>• Pooled Risk Difference: -1.89 (95% CI: -11.50 to 7.72)<br>• Pooled Risk Ratio: 0.41 (95% CI: 0.05 to 3.27) | | |
| | | | Total: 2 studies<br>RCT (n=2) | | 7-10 days | | **Febrile seizures**<br>• Pooled incidence:<br>o MMRV: 1.43% (1/700)<br>o MMR: 0% (0/305) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • Pooled Risk Difference: 1.20 (95% CI: -6.30 to 8.69)<br>• Pooled Risk Ratio: 0.80 (95% CI: 0.07 to 9.20) | | |
| | | | Total: 5 studies<br>RCT (n=5) | | 0-42 days | Safety - vaccine-related febrile seizures | **Vaccine-related febrile seizures**<br>• Pooled incidence:<br>o MMRV: 0.20% (1/5119)<br>o MMR: 0% (0/1575)<br>• Pooled Risk Difference: 0.21 (95% CI: -1.91 to 2.33)<br>• Pooled Risk Ratio: 0.47 (95% CI: 0.09 to 2.32) | | |
| | | | Total: 5 studies<br>RCT (n=5) | | 7-10 days | | **Vaccine-related febrile seizures**<br>• Pooled incidence:<br>o MMRV: 0.20% (1/5119)<br>o MMR: 0% (0/1575)<br>• Pooled Risk Difference: 0.21 (95% CI: -1.91 to 2.33)<br>• Pooled Risk Ratio: 0.47 (95% CI: 0.09 to 2.32) | | |
| | | **Second dose quadrivalent MMRV plus other vaccines**<br>(Brand not specified) | Total: 1 study<br>RCT (n=1) | Other vaccines | 0-28 days | Safety - febrile seizures | **Febrile seizures**<br>• Incidence:<br>o MMRV + others: 0% (0/347)<br>o Others: 0% (0/1453)<br>• Risk Difference: 0 (95% CI: -4.09 to 4.09)<br>• Risk Ratio: 4.18 (95% CI: 0.08 to 210.43) | | |
| | | | Total: 1 study<br>RCT (n=1) | | 7-10 days | | **Febrile seizures**<br>• Incidence:<br>o MMRV + others: 0% (0/347)<br>o Others: 0% (0/1453)<br>• Risk Difference: 0 (95% CI: -4.09 to 4.09)<br>• Risk Ratio: 4.18 (95% CI: 0.08 to 210.43) | | |
| | | | Total: 1 study<br>RCT (n=1) | | 0-28 days | Safety - vaccine-related febrile seizures | **Vaccine-related febrile seizures**<br>• Incidence:<br>o MMRV + others: 0% (0/347)<br>o Others: 0% (0/1453)<br>• Risk Difference: 0 (95% CI: -4.09 to 4.09) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • Risk Ratio: 4.18 (95% CI: 0.08 to 210.42) | | |
| | | | Total: 1 study<br>RCT (n=1) | | 7-10 days | | **Vaccine-related febrile seizures**<br>• Incidence:<br>o MMRV + others: 0% (0/347)<br>o Others: 0% (0/1453)<br>• Risk Difference:<br>0 (95% CI: -4.09 to 4.09)<br>• Risk Ratio:<br>4.18 (95% CI: 0.08 to 210.42) | | |
| | | **At least one dose quadrivalent MMRV** (in children aged 10-24 mths)<br>ProQuad (n=1 study)<br>Priorix-Tetra (n=2)<br>NR = 1 | Total: 2 studies<br>Retrospective cohort (n=2) | MMR | 7-10 days | Safety - seizure | **Seizure**<br>• Relative Risk (RR) (95% CI)<br>o Study 1: RR 3.21 (2.20 to 4.67)<br>o Study 2: RR 1.90 (1.43 to 2.53)* | | |
| | | | Total: 2 studies<br>Retrospective cohort (n=2) | | 0-42 days | | **Seizure**<br>• Relative Risk (RR) (95% CI)<br>o Study 1: RR 2.91 (1.77 to 2.71)<br>o Study 2: RR 1.40 (1.19 to 1.65)* | | |
| | | | Total: 1 study<br>Retrospective cohort (n=1) | | 7-10 days | Safety - febrile seizure | **Febrile seizure**<br>• Adjusted Relative Risk (95% CI): 2.36 (1.03 to 5.38) | | |
| | | | Total: 2 studies<br>Retrospective cohort (n=1); Matched cohort (n=1) | | 5-12 days | | **Febrile seizure**<br>• Pooled Relative Risk (95% CI): 2.32 (1.49 to 3.60) | | |
| | | | Total: 2 studies<br>Retrospective cohort (n=1); Matched cohort (n=1) | | 0-42 days | | **Febrile seizure**<br>• Pooled Relative Risk (95% CI): 1.27 (0.98 to 1.66) | | |
| | | **At least one dose quadrivalent MMRV** (in children aged 4-6yrs)<br>ProQuad (n=1) | Total: 1 study<br>Retrospective cohort (n=1) | MMR | 7-10 days | Safety - seizure | **Seizure**<br>• Relative Risk (95% CI): 2.46 (0.76 to 7.97) | | |
| | | | Total: 1 study<br>Retrospective cohort (n=1) | | 0-42 days | | **Seizure**<br>• Relative Risk (95% CI): 1.06 (0.65 to 1.73) | | |

*Study was not included in the pooled analysis due to the same data source with others;
Key: MMRV – measles, mumps, rubella, varicella; MMR – measles, mumps, rubella; NA – not applicable; NR - not reported; RR – relative risk; VE - vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Marin<br><br>2019<br><br>10.1542/peds.2019-1305.<br><br>Not funded; One of the authors received National Institutes of Health funding (R01DK03094) and had a contractual relationship with Merck through the Varicella Zoster Virus Identification Program.<br><br>The authors have indicated they have no financial relationships relevant to this article to disclose<br><br>From database inception to 31 December 2018 | Immunocompetent children who received varicella vaccine<br><br>12 index cases and 12 secondary cases in households (n=11) and school (n=1) | **1st dose of mostly monovalent Varivax** (exact numbers not reported). | Total: 2 studies (Study type NR) | NA | Various | Safety - vOka transmission from a varicella vaccine recipient who developed a varicella-like rash soon after vaccination | **Safety - vOka transmission from vaccine recipient with varicella-like rash**<br>Case #1:<br>• 1yr old developed 2 vesicular lesions 14 days post-vaccination (index case).<br>• 4mth old sibling developed a rash with 25 lesions 19 days after index case rash onset (vOka laboratory confirmed).<br><br>Case #2:<br>• 1yr old developed 12 vesicular lesions 17 days post-vaccination.<br>• 35yr old father developed >100 lesions 17 days after index case rash onset (vOka laboratory confirmed).<br><br>Case #3:<br>• 1yr old developed ~30 vesicular lesions 24 days post-vaccination.<br>• 30yr old pregnant mother (gestation 5-6 wks) developed 100 vesicular lesions with no fever 16 days after index case rash onset (vOka laboratory confirmed).<br>• Mother terminated the pregnancy. Fetal tissue was negative for VZV by PCR. | Healthy, vaccinated persons have minimal risk for transmitting vOka to contacts and only if a rash is present. Secondary cases of varicella caused by vOka have been typically mild. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | | Total: 5 studies (Study type NR) | NA | Various | vOka transmission from a varicella vaccine recipient who developed vOka herpes zoster (HZ) after vaccination | **vOka transmission from vaccine recipient with HZ**<br>Case #1:<br>• 20mth old developed HZ 5mths after varicella vaccination.<br>• 35yr old father developed a generalized varicella-like rash, positive for vOka, with an | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | uncountable number of lesions 14 days after HZ onset; father reported varicella in childhood.<br><br>Case #2:<br>• 3yr old developed HZ 2 yrs after varicella vaccine.<br>• 2yr old unvaccinated brother had a rash with 10-20 papulovesicles and fever 19 days after HZ onset.<br>• DNA sequence of skin lesion specimens from the brother matched those of vOka in vaccine received by his older sibling.<br><br>Case #3:<br>• 5yr old developed HZ 13 mths after varicella vaccination.<br>• 23yr old teacher developed varicella with 50–100 vesicular lesions and a 1-day, low grade fever 17 days later after HZ onset.<br>• Molecular typing of DNA from vesicular fluid from the teacher's rash showed vOka with the same characteristics as the vaccine received by the child.<br><br>Case # 4:<br>• 3yr old developed HZ 5 mths after varicella vaccination.<br>• Brother (age not reported) who received varicella vaccine at the same time developed ~50 vesicular lesions 14 days after HZ onset in his sibling.<br>• Virus isolated from brother's skin lesions was confirmed as vOka.<br><br>Case #5:<br>• 2yr old developed HZ 8 mths after varicella vaccination (MMRV vaccine). | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • 28yr old mother developed a maculopapular and vesicular rash in a nondermatomal distribution 2 weeks after HZ onset.<br>• Mother also had mild meningismus but no focal neurologic signs. Cerebrospinal fluid culture result was positive for VZV; vOka was identified in skin lesion specimens from both daughter and mother. | | |
| | | | Total: 4 studies (Study type NR) | NA | Various | Unconfirmed vOka transmission (due to no or insufficient laboratory testing performed to document vOka) | **Unconfirmed vOka transmission**<br>Case #1:<br>• 15mth old developed vesicular rash 1 week post-vaccination.<br>• 51yr old household contact of index case with history of renal transplant; developed "mild varicella" 40 days after vaccination of index case.<br>• Evidence for possible vOka transmission includes seroconversion, positive result of tzanck smear of lesion, clinical varicella.<br><br>Case #2:<br>• 2yr old with no post-vaccination rash reported.<br>• Immunocompetent father with history of 10-day course of high-dose steroids for musculoskeletal pain developed varicella with hepatitis 3 weeks after son's vaccination.<br>• No direct exposure of the father to the virus was identified.<br>• Evidence for possible vOka transmission includes positive VZV PCR result from lesion (not typed), clinical varicella.<br><br>Case #3: | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • 9mth old with generalized nonvesicular rash 1 week post-vaccination.<br>• Mother developed mild varicella (<30 lesions) 11 days after daughter's vaccination; no laboratory testing was done.<br>• Evidence for possible vOka transmission includes clinical varicella.<br><br>Case #4:<br>• 2 children (ages not reported) vaccinated with no post-vaccination rash reported.<br>• 32yr old pregnant mother (gestation 39 weeks) developed generalised maculopapular vesicular pustular rash 6 days after her children were vaccinated.<br>• Evidence for possible vOka transmission includes clinical varicella. | | |

Key: HZ – herpes zoster; MMRV – measles, mumps, rubella, varicella; NA – not applicable; NR - not reported; PCR – polymerase chain reaction; VE - vaccine effectiveness; vOka – varicella vaccine Oka strain;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| New Zealand National Health Committee<br><br>2012<br><br>DOI: NR; Link: https://www.moh.govt.nz/notebook/nbbooks.nsf/0/1BA074BCCABF911ACC257F7F000A4101/$file/nhc-varicella-vaccine-assessment-report.pdf<br><br>Funding: Review conducted by an independent statutory authority<br><br>1 January 2009 to 16 September 2011 (HTA Agency & repositories); to 2 November 2011 (MEDLINE & Cochrane and 16 November 2011 (EMBASE) | Children aged 0-5yrs | **One-dose**<br>(vaccine type NR) | Total: 1 study<br>Study type NR | NR | NR | Safety (herpes zoster) | **Safety - herpes zoster**<br>• At the individual level, most studies suggest that the risk of HZ following a single dose varicella vaccination is lower than the risk following wild-type varicella infection. | Evidence suggests that all single-antigen vaccines currently available for varicella are clinically safe for most children aged 15 months and 4 years, alongside existing immunisations on the schedule. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | **Two-dose quadrivalent MMRV** | Total: 1 study<br>RCT (n=1) | Interval between doses | NR | Safety of varicella vaccine (tolerance) | **Safety - tolerance**<br>• 2-doses of MMRV vaccine administered in the second year of life were well tolerated whether administered with a dose interval of 4 weeks or 12 months. | | |
| | | **At least one-dose monovalent and quadrivalent MMRV**<br>Varivax (1 study)<br>(Dosage NR) | Total: 2 studies<br>Study type: NR | NA | 5yrs after vaccination (1 study) | Safety of varicella vaccine (death, local reactions, febrile seizures (MMRV), fever and mild papulovesicular rash) | **Safety - various**<br>• While there are instances of morbidity directly related to the use of both the single-antigen and combined MMRV vaccines, there do not appear to be any deaths. Experience internationally, suggests the following adverse reactions are possible: local reactions, febrile seizures (MMRV), fever and mild papulovesicular rash.<br>• Five-year results of the European Varicella Zoster Virus Identification Programme continue to confirm that Oka/Merck vaccine is generally well tolerated. | | |
| | | **At least one-dose quadrivalent MMRV**<br>(Dosage NR) | Total: 1 study<br>RCT: n=1 | NR | NR | Safety of varicella vaccine (tolerance) | **Safety - tolerance**<br>• MMRV vaccine is well tolerated when administered either subcutaneously or intramuscularly to children in the 2nd year of life. | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | Total: 2 studies<br>RCTs: n=2 | Co-administration with other vaccines (tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine, PHiD-CV) | NR | Safety of varicella vaccine (tolerance) | **Safety - tolerance**<br>• Co-administration of MMRV with tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine during the 2nd yr of life has shown to be well tolerated.<br>• MMRV and PHiD-CV vaccine can be co-administered without compromising the safety profile of either vaccine. | | |

Key: MMRV - measles, mumps, rubella, varicella; MMR+V - measles, mumps, rubella vaccine and varicella vaccine administered concomitantly; NR - not reported; PHiD-CV - pneumococcal conjugated vaccine; USA - United States of America; VE - vaccine effectiveness

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Pallas<br><br>2011<br><br>DOI: Not published<br><br>Funding: Systematic review commissioned by the ECDC and conducted by Pallas Health Research Consultancy, Rotterdam, the Netherlands. An ECDC report partially updated this systematic review with searches up until 8 June 2012, with one new study relevant for the current overview of reviews identified. For completion, the single relevant additional study is added here.<br><br>Pubmed:<br>1 September 1995 to 1 September 2010 | Human subjects vaccinated with VZV vaccine | **One-dose monovalent MMR+V**<br>(various brands) | Total: 1 study<br>RCT (n=1) | MMR | NR | Safety<br>(any adverse event) | **Safety (any adverse event)**<br>• Proportion of children experiencing at least one adverse event did not differ considerably between recipients MMR+V (75.6%) and MMR (78.0%).<br>• No vaccine-related serious adverse experiences were reported. | The safety of monovalent varicella vaccines and quadrivalent MMRV vaccines seem to be supported sufficiently by a large amount of evidence. However, due to large heterogeneity between studies, it is often difficult to summarise the evidence. | **Risk of bias**<br>The methodological quality of the articles were, when possible, critically appraised using the Evidence Based Medicine CoCanCPG checklists, specific for each study design. However, no results presented for included studies.<br><br>**Overall quality of evidence assessment**<br>No overall quality of evidence assessment undertaken. If available, the level of evidence of included studies was graded and reported in Evidence Tables using a grading system for evidence-based medicine developed by the Dutch |
| | | | Total: 2 studies<br>RCTs (n=2) | | | Safety<br>(short-term effects of vaccination – local adverse events) | **Safety (local adverse events)**<br>• Both studies reported a higher incidence of injection-site adverse events at varicella vaccine injection sites than at MMR-injection sites.<br>• 1 study reported higher incidence of injection-site adverse events when MMR+V is given concomitantly than 6 weeks apart. | | |
| | | | Total: 3 studies<br>RCT (n=2)<br>Feasibility (n=1) | | | Safety<br>(short-term effects of vaccination – local adverse events: pain, redness and swelling) | **Safety (pain, redness, swelling)**<br>• The findings of these studies suggest that pain, redness and swelling are more frequent at varicella vaccine injection sites than at MMR-injection sites (n=2 studies).<br>• No differences were observed between monovalent varicella vaccine types (n=1 study). | | |
| | | | Total: 4 studies<br>RCT (n=4) | | | Safety<br>(systemic adverse events) | **Safety (systemic adverse events)**<br>• Systemic adverse events observed in 28.1-73.0% of the study population vaccinated with MMR+V and in 60.0-69.2% of the population vaccinated with MMR. | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Embase:<br>1995 to 2011<br><br>Cochrane Library:<br>2000 to 2010 | | | | | | | • Comparable proportions of specific systemic adverse experiences during days 1 to 43 after vaccination in MMR+V (59.1%) and MMR (60.0%) recipients. | | Insititute for Healthcare Improvement (CBO). |
| | | | Total: 5 studies<br>RCT (n=5) | | | Safety (systemic adverse events – fever and rash) | **Safety (fever and rash)**<br>• Fever and rash were not different between recipients of MMR+V and MMR. Rashes were reported very infrequently (n=3 studies).<br>• 1 study reported a slightly higher incidence of fever in recipients of varicella vaccine and MMR (MMR+V) than in recipients of MMR.<br>• 1 study reported that fever (≥38.8°C) occurred in 9.4% of all MMR+V recipients and 9.9% of all MMR recipients.<br>• 1 study reported on the incidence of fever in Australian children receiving MMR+V (66.2%) and MMR (55.8%) vaccine only. They also reported that rash occurred in 39% of all MMR+V recipients and in 29.9% of all MMR recipients. | | |
| | | **Two-dose monovalent (Varivax)** | Total: 1 study<br>RCT (n=1) | NA | NR | Safety (systemic adverse events) | **<u>Safety (systemic adverse events)</u>**<br>• 1 study reported the most common systemic events that occurred after a booster dose of varicella vaccine including: upper respiratory infections (44.4%), cough (37.0%), irritability or nervousness (28.6%), disturbed sleep (22.9%) and fatigue (21.7%). Varicella like rashes occurred in 1.0% of all vaccinations. | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | **One-dose quadrivalent MMRV** | Total: 1 study<br>RCT (n=1) | MMR | NR | Safety<br>(any adverse event) | **Safety (any adverse event)**<br>• Proportion of children experiencing at least one adverse event did not differ considerably between recipients of MMRV (77.6%) and MMR (78.0%).<br>• No vaccine-related serious adverse experiences were reported. | | |
| | | | Total: 2 studies<br>RCT (n=2) | | | Safety<br>(local adverse events) | **Safety (local adverse events)**<br>• Two studies reported no difference in the frequency of local adverse events between recipients of MMRV and MMR.<br>• One study found that swelling occurred more in MMRV recipients than MMR recipients although evidence is not conclusive. | | |
| | | | Total: 4 studies<br>RCT (n=4) | | | Safety<br>(systemic adverse events) | **Safety (systemic adverse events)**<br>• In general, systemic adverse events were observed in 33.0-75.1% of the study population vaccinated with 1-dose MMRV and 60-69.2% of the study population vaccinated with MMR.<br>• Comparable proportions of specific systemic adverse experiences during days 1 to 43 after vaccination in MMRV (54.7%) and MMR (60.0%) and recipients. | | |
| | | | Total: 2 studies<br>RCT (n=2) | | | Safety<br>(systemic adverse events: fever and rash) | **Safety (fever and rash)**<br>• 1 study reported that fever (≥38.8 ℃) occurred in 10.2% of all MMRV recipients and 9.9% of all MMR recipients.<br>• 1 study reported on the incidence of fever in Australian children receiving MMRV (70.9%) vaccines and MMR (55.8%) vaccine only. They also reported that rash occurred in 34.2% of all MMRV | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | recipients and in 29.9% of all MMR recipients. | | |
| | | **Two-dose quadrivalent MMRV** | Total: 2 studies<br>RCT (n=1);<br>Review (n=1) | MMR | NR | Safety (local adverse events: pain) | **Safety (pain)**<br>• After a 2nd dose of either MMRV or MMR, a significantly higher proportion of subjects experience pain in the MMRV group. | | |
| | | | Total: 3 studies<br>RCT (n=2);<br>Review (n=1) | | | Safety (local adverse events: redness and swelling) | **Safety (redness and swelling)**<br>• 2nd dose of MMRV significantly increased the likelihood of developing redness compared with a 2nd dose of MMR.<br>• 2nd dose of MMRV or MMR tends to result in higher incidence of swelling in recipients of MMRV than in recipients of MMR, although evidence is not conclusive. | | |
| | | | Total: 2 studies<br>RCT (n=2); | | | Safety (systemic adverse events) | **Safety (systemic adverse events)**<br>• In general, systemic adverse events were observed in 37.6-66.2% of the study population vaccinated with a 2nd dose of MMRV and 60-69.2% of the study population vaccinated with MMR. | | |
| | | | Total: 4 studies<br>RCT (n=3);<br>Review (n=1) | | | Safety (systemic adverse event: fever) | **Safety (fever)**<br>• Incidence of fever after 2nd dose did not differ between groups. | | |
| | | **At least one-dose monovalent or quadrivalent MMRV** | Total: 5 studies<br>RCT (n=5); | MMR | NR | Safety (systemic adverse events) | **Safety (systemic adverse events)**<br>• Overall, the included studies showed that the proportion of subjects with systemic adverse events was comparable in vaccination groups. | | |
| | | | Total: 2 studies<br>RCT (n=2) | | | Safety (systemic adverse events: fever) | **Safety (fever)**<br>• The incidence of fever following varicella vaccination | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | (MMRV or MMR+V) is higher than following vaccination with MMR. | | |
| | | **Two-dose quadrivalent MMRV** | Total: 3 studies RCT (n=3) | One-dose quadrivalent MMRV | NR | Safety (general and specific adverse events) | **Safety (general and specific adverse events)**<br>• Overall proportion of subjects with injection-site adverse events was lower (almost half) in subjects who received 2nd dose of MMRV compared with 1st dose. | | |
| | | | Total: 3 studies RCT (n=3) | | | Safety (systemic adverse events) | **Safety (systemic adverse events)**<br>• Incidence of systemic adverse events was similar among recipients of 1- or 2-doses of MMRV vaccine. | | |
| | | | Total: 7 studies RCT (n=6); Review (n=1) | | | Safety (systemic adverse events: fever) | **Safety (fever)**<br>• Incidence of fever lower after 2nd dose of MMRV compared with 1st dose but not different between groups. | | |
| | | | Total: 3 studies RCT (n=3) | | | Safety (systemic adverse events: rash) | **Safety (rash)**<br>• Rash appears to occur less frequently after 2nd dose of MMRV compared to 1st dose. | | |

Key: BV – breakthrough varicella; CoCanCPG - Coordination of Cancer Clinical Practice Guidelines; ECDC - European Centre for Disease Prevention and Control; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; MMR+V – measles, mumps, rubella vaccine and varicella vaccine administered concomitantly; NR – not reported; RCT – randomised controlled trial; SR – systematic review; VE – vaccine effectiveness;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Panozzo<br><br>2019<br><br>10.1016/j.vaccine.2018.06.067<br><br>Partially supported by the World Health Organization (WHO)<br><br>From database inception to 28 May 2015 for searches except Pubmed (to 3 December 2017) | Protocol:<br>Individuals experiencing arthritis and/or arthralgia following immunisation<br><br>Included study:<br>Privately insured children, 12-23mths of age; (USA, 2000–2012) | **At least one-dose (monovalent and quadrivalent)**<br>Varivax (Merck) monovalent vaccine and MMRV quadrivalent (unspecified): 1 study*<br><br>*Both vaccines included in the same study | Total: 1 study<br>Retrospective cohort (n=1) | NA | Up to 180 days | Safety - arthritis or arthralgia (composite outcome) | **Safety - cases of arthritis or arthralgia**<br>• Doses administered:<br>o MMRV: 123,200<br>o MMR+V: 584,987<br>• Number of cases:<br>o 1 case of arthritis/arthralgia after MMRV and 1 case after MMR+V 1-42 days post-vaccination in primary analyses<br>o 1 case of arthritis/arthralgia after MMRV and 3 cases after MMR+V 1-42 days post-vaccination in secondary analyses<br>o 6 cases of arthritis/arthralgia after MMRV and 25 cases after MMR+V 57-180 days post-vaccination in secondary analyses.<br>• Primary analyses used stratified exact binomial tests and secondary analyses used case-centered logistic regression | The current evidence linking vaccination to incident arthritis or worsening of arthritic conditions is too heterogeneous and incomplete to infer a causal association. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

Key: MMRV – measles, mumps, rubella, varicella; MMR+V – measles, mumps, rubella vaccine and varicella vaccine administered concomitantly; NA – not applicable; NR - not reported; VE - vaccine effectiveness; WHO – World health Organization;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Phuong<br><br>2017<br><br>10.1016/j.vaccine.2016.09.033<br><br>Italian Medicines Agency (AIFA)<br><br>From database inception to June 2016 | Kawasaki disease cases following vaccination | **At least one dose quadrivalent**<br>Brand not specified | Total: 1 study<br><br>Retrospective cohort (n=1) | NA | NR | Safety - Kawasaki Disease | **Safety – Kawasaki Disease (KD)**<br>• A cohort study used the US Vaccine Safety Datalink data to assess adverse effects associated with MMRV vaccines. The study estimated an incidence of 1 KD case per 11,824 doses of MMRV and concluded that MMRV was not associated with an increased risk of KD.<br>• No clinical features or diagnostic criteria regarding this one KD case were provided. | The authors concluded that MMRV was not associated with an increased risk of KD | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>Not conducted |

Key: AIFA – Italian Medicines Agency; KD – Kawasaki disease; MMRV – measles mumps, rubella, varicella; NA – not applicable; NR – not reported; US – United States;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Skull<br><br>2001<br><br>10.1136/adc.85.2.83<br><br>Funding: NR<br><br>1966 to December 2000 | Human subjects vaccinated with VZV vaccine | **One-dose**<br>(vaccine type NR) | Total: 21 studies<br>RCTs (n=6)<br>Prospective cohort (n=14)<br>Post-licensure study (n=1) | Placebo and no vaccination | Up to 7yrs (1 RCT)<br>1 to 19.6yrs (cohort studies) | Safety (deaths) | **Safety - deaths**<br>• Although controlled trials confirm approximately 100% relative risk reduction for severe disease, no deaths have been reported for subjects in either vaccine or placebo groups.<br>• A post-licensure report found 14 deaths temporally related to 9.7 million doses of varicella vaccine; of the five presented case reports, none had proven vaccine strain VZV. There is therefore no direct evidence to support or refute a risk reduction in varicella mortality consequent to use of varicella vaccine, although available evidence suggests a reduction is likely. | This critical review has found strong evidence for the effectiveness of VZV vaccination in the prevention of varicella in children. | **Risk of bias**<br>Studies were systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care. The results for individual studies are not provided.<br>The quality of evidence in studies included in this analysis was reported as generally good. However, the following methodological issues were identified.<br><br>Loss of subjects from analysis was sometimes considerable, particularly where the duration of follow up was ≥7yrs. Other trials relied on self reporting of VZV disease to investigators, while occasional studies |
| | | **One-dose**<br>(vaccine type NR) | Total: 21 studies<br>RCTs (n=6)<br>Prospective cohort (n=14)<br>Post-licensure study (n=1) | Placebo and no vaccination | Up to 7yrs (1 RCT)<br>1 to 19.6yrs (cohort studies) | Safety (deaths) | **Safety - deaths**<br>• Although controlled trials confirm approximately 100% relative risk reduction for severe disease, no deaths have been reported for subjects in either vaccine or placebo groups.<br>• A post-licensure report found 14 deaths temporally related to 9.7 million doses of varicella vaccine; of the five presented case reports, none had proven vaccine strain VZV. There is therefore no direct evidence to support or refute a risk reduction in varicella mortality consequent to use of varicella vaccine, although available | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | evidence suggests a reduction is likely. | | followed only vaccinees who initially seroconverted. These biases could potentially result in an over estimation of VE by underestimating the true number of cases. However, outcomes across studies were consistent regardless of study design or duration of follow up, suggesting a true effect.<br>**Overall quality of evidence assessment**<br>Using the Canadian Task Force on Preventive Health Care methodology, there was deemed Good evidence to include immunisation of 12-15mth old children with varicella vaccine to prevent varicella infection and secondary cases in household contacts. This was based on |
| | | **2nd dose (vaccine type NR)** | Total: 3 studies<br>Study type: NR | 1st dose (vaccine type NR) | NR | Safety (reactions) | **Safety - reactions**<br>• A second dose of vaccine appears to cause fewer reactions than the first. | | |
| | | **NR** | Total: 3 studies<br>RCT (n=3) | Placebo | NR | Safety (short-term effects) | **Safety - short-term effects**<br>• 3 RCTs in children showed no increase in rates of fever or varicella like rash. Rates of fever varied from 0% to 36% depending on the definition of fever and the duration of follow up. Less than 5% of vaccine and placebo recipients experienced a mild, varicella like rash.<br>• 1 RCT found an increase in local reactions (mild and well tolerated) in vaccine recipients while another smaller trial found no difference. Injection site reactions occurred in 7–30% of study participants. | | |
| | | **NR** | Total: NR<br>Study type (RCT, nRCT, post licensure study) | Placebo | NR | Safety (serious adverse events) | **Safety - serious adverse events**<br>• No serious adverse events have been reported in controlled trials.<br>• 1 post-licensure review of 89,000 vaccinees found no serious reactions while another found a temporally related serious adverse event rate of 2.9/100,000 doses. | | |
| | | **Unclear**<br>Oka/Merck vaccine reported for some studies | Total: 13 studies<br>RCT (n=1);<br>Prospective cohort (n=1);<br>Other cohort (n=8);<br>Case series: (n=1); | Placebo | Uo to 9mths for RCT<br><br>Up to 19yrs 7mths for cohort studies | Safety (herpes zoster) | **Safety - herpes zoster**<br>• In 1 RCT, no cases of herpes zoster were noted in either placebo or vaccine recipients after 9mths (732 person yrs).<br>• A single prospective cohort study of children has reported a mild case of zoster in 1 of | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | Post-licensure adverse event reporting system (n=1);<br>Unknown: (n=1); | | | | 854 children after vaccination (duration of follow up unknown).<br>• 7 other cohort studies report no zoster for as much as 19yrs 7mths, or 3277 person years after vaccination.<br>• Two mild cases of zoster (no virus isolated) were reported in healthy children (aged 2 and 4 yrs) following vaccination with Oka/Merck vaccine and a rate of 21 cases/100,000 person-yrs was estimated for Oka/Merck recipients to that time, compared with an expected rate of 77/100,000 person yrs in school aged children following natural chickenpox.<br>• In 1992, it was estimated that 14 cases per 100,000 vaccinees (all mild) had occurred over 9yrs of Oka/Merck vaccination in the USA.<br>• A population based study over a longer period found a rate of 42/100,000 in unvaccinated children (20/100,000 in children under 5yrs).<br>• The US post-licensure Vaccine Adverse Event Reporting System suggests a rate of 2.6/100,000 vaccine doses distributed. | | Level I Evidence provided from 6 well designed RCTs and Level II-I Evidence from 12 well designed cohort studies. |
| | | **NR** | Total: 5 Studies<br>Study type:<br>RCT (n=1),<br>nRCT (n=1),<br>Case report (n=1),<br>Post licensure study (n=1)<br>Other (n=1) | Placebo | NR | Safety (varicella transmission from vaccinated individuals) | **Safety - varicella transmission from vaccinated individuals**<br>• No clinical trials have shown transmission of vaccine related VZV between immunocompetent individuals.<br>• One placebo controlled RCT found seroconversion, but no disease in 3/439 placebo vaccinated siblings of 465 VZV | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | vaccine recipients. Natural infection or subclinical spread of vaccine virus may have occurred.<br>• In a small controlled trial, no evidence of transmission or boosting in unvaccinated seronegative and seropositive close contact were found.<br>• Case report of transmission has been reported rarely from children with varicella like rash following vaccination.<br>• Reported transmission of vaccine strain virus from a vaccinated child with zoster to their vaccinated sibling, resulting in mild chickenpox.<br>• A post-licensure report using passive surveillance methods has also found very few cases of possible vaccine strain transmission ("mostly unconfirmed by PCR"). | | |

Key: NR – not reported; nRCT – non-randomised controlled trial;PCR – polymerase chain reaction; RCT – randomised controlled trial; VE – vaccine effectiveness; VZV – varicella zoster virus;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Van den Boogaard<br><br>2021<br><br>10.1016/j.vaccine.2020.12.079<br><br>World Health Organization<br><br>1 January 2010 to 17 May 2019 | Immunocompetent individuals, without known hypersensitivity reactions to vaccine-components | **At least one-dose** of varicella vaccine administered alongside rubella containing vaccines (RCV) | Total: 3 studies<br>Case report (n=3) | NA | Various | Occurrence of severe adverse events (SAEs) as defined by the primary authors, including febrile convulsions, thrombocytopenic purpura and arthritis, with a focus on rarely reported/uncommon SAEs. | **Safety – severe adverse events**<br><br>Case report #1: Vaccine-induced thrombocytopenic purpura in a 15mth old girl 12 days after sequential administration of measles, rubella, varicella and mumps vaccination with intervals of 4 weeks.<br><br>Case report #2: Case of high fever 1 day after MMRV vaccination and seizures 6 days later in a 13mth old girl.<br><br>Case report #3: First episode of temporary 6th nerve palsy after MMR vaccination, 2nd episode after varicella vaccination. | One and two doses of rubella containing vaccine are safe.<br><br>Several studies pointed towards a higher risk of febrile convulsions after MMRV than after MMR vaccination. Since the focus of our review was not on varicella-containing vaccines, this effect should be further reviewed. | **Risk of bias**<br>Not conducted<br><br>**Overall quality of evidence assessment**<br>GRADE Quality of Evidence assessment applied for all study types (incl. case reports over) examining serious adverse events after 1 or 2 doses of RCV.<br>Certainty of evidence rated as MODERATE. |

Key: MMR – measles, mumps, rubella; MMRV – measles mumps, rubella, varicella; NA – not applicable; RCV – rubella containing vaccine; WHO – World Health Organization;

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| Author<br>Year<br>DOI<br>Funding source<br>Search dates | Population size<br>Demographics at baseline<br>Setting(s)<br>Location(s) | Vaccine type<br>Vaccine dosage<br>Vaccine brand | Number of studies<br>Study type | Comparator(s) | Follow-up period after vaccination | Efficacy/effectiveness outcomes<br>Safety outcomes | Summary of main findings | From abstract or elsewhere | Yes/No and details if applicable |
| Yin<br><br>2018<br><br>doi.org/10.1080/14760584.2018.1433999<br><br>Natural Science Foundation of Guangdong Province, China<br><br>1995 to June 2017 | Immunocompetent children in America, Singapore, Germany, Belgium, Netherlands, Finland, France, Taiwan, and India (n=904 to 2,048) | **2nd dose monovalent** | Total: 1 study<br>**Self-control** (n=1) | 1st dose monovalent | 0-42 days after vaccination | Safety: Generalised reactions | **RR for incidence of fever of any intensity (95% CI)**<br>RR 0.73 (0.57 to 0.93)<br>**RR for incidence of varicella-like rash (95% CI)**<br>RR 0.40 (0.21 to 0.78) | Safety profiles showed two-dose vaccination was well tolerated but incidence of grade 3 redness and swelling of any intensity was significantly higher compared to one-dose. | **Risk of bias**<br>Risk of bias conducted for all primary studies. Quality scores showed that the quality of all RCTs was high and that the quality of all eligible case–control studies and retrospective cohort studies was ≥7 stars, indicating that the quality of these studies was also good. The modified NOS score of the self-control studies ranged from 5 to 6 stars.<br><br>**Overall quality of evidence assessment**<br>Not conducted |
| | | **2nd dose monovalent** | Total: 1 study<br>**Self-control** (n=1) | 1st dose monovalent | 0-42 days after vaccination | Safety: Generalised reactions | **RR for incidence of fever of any intensity (95% CI)**<br>RR 0.73 (0.57 to 0.93)<br>**RR for incidence of varicella-like rash (95% CI)**<br>RR 0.40 (0.21 to 0.78) | | |
| | | **2nd dose quadrivalent MMRV** | Total: 5 studies<br>**Self-control** (n=5) | 1st dose quadrivalent MMRV | 0-14 days after vaccination | Safety: Generalised reactions | **Pooled RR for incidence of fever (any intensity) (95% CI)**<br>RR 0.59 (0.54 to 0.64) | | |
| | | | Total: 6 studies<br>**Self-control** (n=6) | | 0-42 days after vaccination | | **Pooled RR for incidence of fever (any intensity) (95% CI)**<br>RR 0.73 (0.69 to 0.71)<br>Note: Data extracted as reported in systematic review, but 95% CIs do not appear correct. | | |
| | | | Total: 5 studies<br>**Self-control** (n=5) | | 0-14 days after vaccination | | **Pooled RR for incidence of fever (Grade 3 or ≥ 39.5) (95% CI)**<br>RR 0.32 (0.24 to 0.44) | | |
| | | | Total: 4 studies<br>**Self-control** (n=4) | | 0-42 days after vaccination | | **Pooled RR for incidence of fever (Grade 3 or ≥ 39.5) (95% CI)**<br>RR 0.61 (0.46 to 0.83) | | |
| | | | Total: 4 studies<br>**Self-control** (n=4) | | 0-42 days after vaccination | | **Pooled RR for incidence of varicella-like rash (95% CI)**<br>RR 0.32 (0.16 to 0.62) | | |
| | | **2nd dose quadrivalent MMRV** | Total: 6 studies<br>**Self-control** (n=6) | 1st dose quadrivalent MMRV | 0-3 days after vaccination | Safety: Localised reactions at the injection site | **Pooled RR for incidence of pain (any) (95% CI)**<br>RR 0.89 (0.73 to 1.08) | | |
| | | | Total: 3 studies<br>**Self-control** (n=3) | | | | **Pooled RR for incidence of pain (Grade 3) (95% CI)**<br>RR 2.05 (0.19 to 22.60) | | |
| | | | Total: 6 studies<br>**Self-control** (n=6) | | | | **Pooled RR for incidence of redness (any) (95% CI)**<br>RR 1.00 (0.88 to 1.14) | | |

| Review Details | Population | Intervention(s) | Primary studies (per intervention) | Comparator(s) (per intervention) | Follow-up (per intervention) | Outcomes assessed (per intervention) | Main findings | Authors conclusions | Risk of bias in primary studies and overall quality of evidence assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | Total: 3 studies<br>**Self-control**<br>(n=3) | | | | **Pooled RR for incidence of redness (Grade 3) (95% CI)**<br>RR 4.93 (1.89 to 12.87) | | |
| | | | Total: 6 studies<br>**Self-control**<br>(n=6) | | | | **Pooled RR for incidence of swelling (any) (95% CI)**<br>RR 1.34 (1.06 to 1.66) | | |
| | | | Total: 3 studies<br>**Self-control**<br>(n=3) | | | | **Pooled RR for swelling (Grade 3) (95% CI)**<br>RR 1.03 (0.30 to 3.54) | | |

Key: MMRV – measles, mumps, rubella, varicella; NR – not reported; RR – relative risk; VE - vaccine efficacy/effectiveness;

# Appendix A5.3 AMSTAR2 Quality Appraisal

| Review Details | AMSTAR 2 Questions | | | | | | | | | | | | | | | | | Overall Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Qu 1 | Qu 2 | Qu 3 | Qu 4 | Qu 5 | Qu 6 | Qu 7 | Qu 8 | Qu 9 | | Qu 10 | Qu 11 | | Qu 12 | Qu 13 | Qu 14 | Qu 15 | Qu 16 | |
| Review Author & Year | Did the research questions and inclusion criteria for the review include the components of PICO? | Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Did the review authors explain their selection of the study designs for inclusion in the review? | Did the review authors use a comprehensive literature search strategy? | Did the review authors perform study selection in duplicate? | Did the review authors perform data extraction in duplicate? | Did the review authors provide a list of excluded studies and justify the exclusions? | Did the review authors describe the included studies in adequate detail? | Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | | Did the review authors report on the sources of funding for the studies included in the review? | If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | | If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? | Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | |
| Amaral_2021 | Yes | No | No | No | No | No | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | No | Critically Low |
| Bauwens_2019 | Yes | No | Yes | Partial Yes | No | Yes | No | Partial Yes | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Benchimol_2021 | Yes | No | Yes | Partial Yes | Yes | Yes | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| DiPietrantonj_202 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | RCTs: Yes | NRSI: Yes | Yes | RCTs: Yes | NRSI: Yes | Yes | Yes | No | Yes | Yes | High |
| Garrido_2012 | Yes | No | No | No | No | No | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | Yes | No | No MA | Yes | Critically Low |
| Gidengil_2021 | Yes | Yes | Yes | Partial Yes | Yes | No | Yes | Partial Yes | RCTs: Partial Yes | NRSI: Partial | Yes | RCTs: No MA | NRSI: No MA | No MA | No | Yes | No MA | Yes | Low |
| Grazina_2020 | Yes | Partial Yes | Yes | Partial Yes | Yes | Yes | Partial Yes | Partial Yes | RCTs: NA | NRSI: Partial | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Low |
| Ma_2015a | Yes | No | No | Partial Yes | Yes | Yes | No | Partial Yes | RCTs: Partial Yes | NRSI: NA | No | RCTs: Yes | NRSI: No MA | No | No | Yes | Yes | Yes | Critically Low |
| Ma_2015b | Yes | No | Yes | Yes | Yes | Yes | No | Yes | RCTs: Partial Yes | NRSI: Partial | No | RCTs: Yes | NRSI: No | No | No | Yes | Yes | Yes | Critically Low |
| Marin_2019 | Yes | No | No | Partial Yes | Yes | Yes | No | No | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| NZ_2012 | Yes | No | Yes | Partial Yes | No | No | No | No | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Pallas_2011 | Yes | No | Yes | No | Yes | Yes | Yes | Yes | RCTs: No | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | Yes | No MA | No | Critically Low |
| Panozzo_2019 | Yes | No | Yes | No | No | Yes | Partial Yes | Yes | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | Yes | No MA | Yes | Critically Low |
| Phuong_2017 | Yes | No | Yes | No | No | No | No | Partial Yes | RCTs: NA | NRSI: No | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Skull_2001 | Yes | No | Yes | Partial Yes | No | No | No | No | RCTs: NA | NRSI: NA | No | RCTs: No MA | NRSI: No MA | No MA | Yes | No | No MA | Yes | Critically Low |
| vandenBoogaard | Yes | No | Yes | No | Yes | No | No | Partial Yes | RCTs: NA | NRSI: NA | No | RCTs: No MA | NRSI: No MA | No MA | No | No | No MA | Yes | Critically Low |
| Yin_2018 | Yes | No | Yes | Partial Yes | Yes | Yes | No | No | RCTs: Partial Yes | NRSI: Partial | No | RCTs: Yes | NRSI: Yes | Yes | Yes | Yes | Yes | Yes | Critically Low |

Key: MA – meta-analysis; NRSI – non-randomised study of intervention ; RCT – randomised controlled trial;

## Appendix A5.4 Excluded Studies

| Study number | Title | Authors | Year Published | DOI / Weblink | Exclusion reason |
|---|---|---|---|---|---|
| 1 | Risk of febrile convulsions after mmrv vaccination in comparison to MMR or MMR + V vaccination | Schink, T.; Holstiege, J.; Edeltraut, G. | 2012 | 10.1002/pds.3324 | Abstract only |
| 2 | Varicella vaccination is associated with increased prevalence of eczema in the US | Silverberg, J.; Li, J. C. | 2015 | 10.1038/jid.2015.70 | Abstract only |
| 3 | The relation between vaccinations and optic neuritis-A literature review | Mailand, M. T.; Frederiksen, J. L. | 2017 | 10.1080/01658107.2017.1353798 | Abstract only |
| 4 | Severe complications of varicella in persons vaccinated with varicella vaccine (breakthrough varicella): A systematic literature review | Leung, J.; Broder, K.; Marin, M. | 2016 | 10.1093/ofid/ofw172.659 | Abstract only |
| 5 | Should varicella vaccination be introduced into the national immunization guidelines? | Nguyen, E.; Baird, O.; Dzulkarnain, M.; Wong, K.; Ali-Bujang, N.; Ooi, S. T.; Kivlehan, R.; Power, C.; Molloy, E.; Meehan, J. | 2019 | 10.1136/archdischild-2019-epa.715 | Abstract only |
| 6 | Varicella vaccination in The United States: Two decades of experience with program implementation | Marin, M.; Lopez, A. S.; Leung, J.; Schmid, D. S.; Harpaz, R. | 2016 | 10.1093/ofid/ofw172.620 | Abstract only |
| 7 | Should varicella vaccination be added to the UK immunisation schedule for healthy children? | Grey, S. J. | 2017 | 10.1136/archdischild-2017-313087.141 | Abstract only |
| 8 | 124 CANADIAN ASSOCIATION OF GASTROENTEROLOGY CLINICAL PRACTICE GUIDELINES ON IMMUNIZATIONS IN INFLAMMATORY BOWEL DISEASE | Benchimol, E. I.; Tse, F.; Carroll, M.; deBruyn, J.; McNeil, S. A.; Pham-Huy, A.; Seow, C. H.; Barrett, L.; Bessissow, T.; Carman, N.; Melmed, G.; Vanderkooi, O.; Marshall, J. K.; Jones, J. L. | 2020 | 10.1016/S0016-5085(20)30738-1 | Abstract only |
| 9 | Acute posterior multifocal placoid pigment epitheliopathy after vaccination: Review of the literature and analysis of the French Pharmacovigilance database | Mangavelle, J.; Damin-Pernik, M.; Bellet, F.; Abadie, D.; Pageot, C.; Beyens, M. N. | 2018 | 10.1111/fcp.12371 | Abstract only |
| 10 | Canadian association of gastroenterology clinical practice guidelines on immunizations in inflammatory bowel disease | Benchimol, E.; Tse, F.; Carroll, M.; DeBruyn, J.; McNeil, S.; Pham-Huy, A.; Seow, C.; Barrett, L.; Bessissow, T.; Carman, N.; Melmed, G.; Vanderkooi, O.; Marshall, J.; Jones, J. | 2021 | 10.1097/MPG.0000000000003177 | Abstract only |
| 11 | Vaccines and Optic Neuritis: A systematic review | Frederiksen, J. L. | 2018 | https://onlinelibrary.wiley.com/doi/epdf/10.1111/ene.13699 | Abstract only |

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| 12 | Safety of Vaccines Used for Routine Immunization in the United States: An update | Aneesa Motala, Susanne Hempel Courtney Gidengil Matthew Goetz Margaret Maglione Owen Hall Jody Larkin Sydne Newberry Christine Chen Nabeel Qureshi Goke Akinniranye | 2020 | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020180089 | Duplicate |
| 13 | Varicella and rotovirus vaccination in New Zealand - assessment reports | New Zealand National Health Committee | 2012 | http://nhc.health.govt.nz/varicella-and-rotovirus-vaccination-new-zealand-assessment-reports | Duplicate |
| 14 | Metaanalysis of vaccine effectiveness in varicella outbreaks | Bayer, O; Heininger, U; Heiligensetzer, C; von Kries, R | 2007 | 10.1016/j.vaccine.2007.07.010 | Duplicate |
| 15 | Varicella vaccination in Italy: an economic evaluation of different scenarios | Coudeville, L; Brunot, A; Giaquinto, C; Lucioni, C; Dervaux, B | 2012 | 10.2165/00019053-200422130-00003 | Duplicate |
| 16 | Vaccination recommendations for Germany | Wiese-Posselt, Miriam; Tertilt, Christine; Zepp, Fred | 2011 | 10.3238/arztebl.2011.0771 | Not a systematic review |
| 17 | Varicella: Efficacy of two-dose vaccination in childhood | Wutzler, P.; Knuf, M.; Liese, J. | 2008 | 10.3238/arztebl.2008.0567 | Not a systematic review |
| 18 | Universal varicella vaccine immunization in Japan | Yoshikawa, Tetsushi; Kawamura, Yoshiki; Ohashi, Masahiro | 2016 | 10.1016/j.vaccine.2016.02.058 | Not a systematic review |
| 19 | Increasing coverage and efficiency of measles, mumps, and rubella vaccine and introducing universal varicella vaccination in Europe: a role for the combined vaccine | Vesikari, Timo; Sadzot-Delvaux, Catherine; Rentier, Bernard; Gershon, Anne | 2007 | 10.1097/INF.0b013e3180616c8f | Not a systematic review |
| 20 | Global impact of varicella vaccination programs | Varela, Fernanda Hammes; Pinto, Leonardo Arajuo; Scotta, Marcelo Comerlato | 2019 | 10.1080/21645515.2018.1546525 | Not a systematic review |
| 21 | Development of varicella vaccine in Japan and future prospects | Ozaki, Takao; Asano, Yoshizo | 2016 | 10.1016/j.vaccine.2016.04.059 | Not a systematic review |
| 22 | Herpes zoster virus sclerokeratitis and anterior uveitis in a child following varicella vaccination | Naseri, A.; Good, W. V.; Cunningham Jr, E. T. | 2003 | 10.1016/S0002-9394(02)01957-8 | Not a systematic review |
| 23 | Varicella vaccination in Australia | Macartney, KK; Beutels, P; McIntyre, P; Burgess, MA | 2005 | 10.1111/j.1440-1754.2005.00717.x | Not a systematic review |
| 24 | Varicella | Heininger, Ulrich; Seward, Jane F | 2006 | 10.1016/S0140-6736(06)69561-5 | Not a systematic review |
| 25 | Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine and Commonly Administered Vaccines After Coadministration | Gasparini, Roberto; Tregnaghi, Miguel; Keshavan, Pavitra; Ypma, Ellen; Han, Linda; Smolenov, Igor | 2016 | 10.1097/INF.0000000000000930 | Not a systematic review |
| 26 | The safety profile of varicella vaccine: a 10-year review | Galea, Susan A; Sweet, Ann; Beninger, Paul; Steinberg, Sharon P; LaRussa, Philip S; Gershon, Anne A; Sharrar, Robert G | 2008 | 10.1086/522125 | Not a systematic review |

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| 27 | Varicella-zoster virus infection: natural history, clinical manifestations, immunity and current and future vaccination strategies | Freer, Giulia; Pistello, Mauro | 2018 | http://www.newmicrobiologica.org/PUB/allegati_pdf/2018/2/95.pdf | Not a systematic review |
| 28 | Review of the Varilrix™ varicella vaccine | Chiu, S. S.; Lau, Y. L. | 2005 | 10.1586/14760584.4.5.629 | Not a systematic review |
| 29 | A literature review regarding the management of varicella-zoster virus | Bond, D.; Mooney, J. | 2010 | 10.1002/msc.175 | Not a systematic review |
| 30 | Live attenuated varicella vaccine | Arvin, Ann M; Gershon, Anne A | 1996 | 10.1146/annurev.micro.50.1.59 | Not a systematic review |
| 31 | Varicella infection in the Middle East: Prevalence, complications, and vaccination | Al-Turab, Mariam; Chehadeh, Wassim | 2018 | 10.4103/jrms.JRMS_979_17 | Not a systematic review |
| 32 | Twelve children with varicella vaccine meningitis: Neuropathogenesis of reactivated live attenuated varicella vaccine virus | Heusel, E. H.; Grose, C. | 2020 | 10.3390/v12101078 | Not a systematic review |
| 33 | Cutaneous adverse reactions following anti-infective vaccinations | Nikkels, A. F.; Nikkels-Tassoudji, N.; PiÃ©rard, G. E. | 2005 | 10.2165/00128071-200506020-00002 | Not a systematic review |
| 34 | Preventing varicella-zoster disease | Hambleton, Sophie; Gershon, Anne A | 2005 | 10.1128/CMR.18.1.70-80.2005 | Not a systematic review |
| 35 | Varicella vaccination of children in the United States: assessment after the first decade 1995-2005 | Grose, Charles | 2005 | 10.1016/j.jcv.2005.02.003 | Not a systematic review |
| 36 | Recommendation on the Use of the Chicken pox Vaccine in Belgium | Conseil supérieur d'Hygiène | 2005 | https://www.nitag-resource.org/sites/default/files/2c1eb376d94d1c96b0ccfc57d206acd7f2c35ecb_1.pdf | Not a systematic review |
| 37 | Varicella infections and varicella vaccine in the 21st century | Vazquez, Marietta | 2004 | 10.1097/01.inf.0000140786.15816.38 | Not a systematic review |
| 38 | Update on varicella | Seward, Jane F | 2001 | 10.1097/00006454-200106000-00014 | Not a systematic review |
| 39 | Live-attenuated varicella vaccine | Gershon, Anne A | 2001 | 10.1016/s0891-5520(05)70268-3 | Not a systematic review |
| 40 | Varicella vaccine: genesis, efficacy, and attenuation | Arvin, Ann M | 2001 | 10.1006/viro.2001.0918 | Not a systematic review |
| 41 | Uveitis associated with varicella virus vaccine | Esmaeli-Gutstein, B.; Winkelman, J. Z. | 1999 | 10.1016/S0002-9394(99)00059-8 | Not a systematic review |
| 42 | Varicella vaccines | Flatt, A.; Breuer, J. | 2012 | 10.1093/bmb/lds019 | Not a systematic review |
| 43 | Varicella-zoster virus | Arvin, Ann M | 1996 | 10.1128/cmr.9.3.361 | Not a systematic review |
| 44 | Varicella vaccine: the Japanese experience | Asano, Yoshizo | 1996 | 10.1093/infdis/174.supplement_3.s310 | Not a systematic review |

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| 45 | CAVEI recommendation for the introduction of varicella vaccine into the National Immunization Programme | CAVEI | 2020 | 10.4067/s0716-10182020000200149 | Not a systematic review |
| 46 | Vaccine associated uveitis | Benage, M.; Fraunfelder, R. W. | 2015 | https://iovs.arvojournals.org/article.aspx?articleid=2335858 | Not a systematic review |
| 47 | Varicella vaccination in Europe - taking the practical approach | Bonanni, Paolo; Breuer, Judith; Gershon, Anne; Gershon, Michael; Hryniewicz, Waleria; Papaevangelou, Vana; Rentier, Bernard; Rumke, Hans; Sadzot-Delvaux, Catherine; Senterre, Jacques | 2009 | 10.1186/1741-7015-7-26 | Not a systematic review |
| 48 | Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: a pooled analysis of r | Bryant, Kristina; McVernon, Jodie; Marchant, Colin; Nolan, Terry; Marshall, Gary; Richmond, Peter; Marshall, Helen; Nissen, Michael; Lambert, Stephen; Aris, Emmanuel; Mesaros, Narcisa; Miller, Jacqueline | 2012 | 10.4161/hv.20357 | Not a systematic review |
| 49 | The effect of vaccination on the epidemiology of varicella zoster virus | Edmunds, WJ; Brisson, M | 2002 | 10.1053/jinf.2002.0988 | Not a systematic review |
| 50 | Pathogenesis and current approaches to control of varicella-zoster virus infections | Gershon, Anne A; Gershon, Michael D | 2013 | 10.1128/CMR.00052-13 | Not a systematic review |
| 51 | Varicella vaccine: the American experience | Gershon, Anne A; LaRussa, Philip; Hardy, lain; Steinberg, Sharon; Silverstein, Saul | 1992 | https://www.jstor.org/stable/30111789 | Not a systematic review |
| 52 | Sixteen years of global experience with the first refrigerator-stable varicella vaccine (Varilrix™) | Kreth, H. W.; Lee, B. W.; Kosuwon, P.; Salazar, J.; Gloriani-Barzaga, N.; Bock, H. L.; Meurice, F. | 2008 | 10.2165/0063030-200822060-00005 | Not a systematic review |
| 53 | Varicella vaccine strain infection in a non-immunocompromised patient. A case report and review of literature | Swed-Tobia, Rana; Kassis, Imad; Hanna, Suhair; Szwarcwort-Cohen, Moran; Dovrat, Sara; Dabaja-Younis, Halima | 2021 | 10.1080/21645515.2020.1802976 | Not a systematic review |
| 54 | Long-term clinical studies of varicella vaccine at a regional hospital in Japan and proposal for a varicella vaccination program | Ozaki, Takao | 2013 | 10.1016/j.vaccine.2013.10.060 | Not a systematic review |
| 55 | Varicella vaccination in Japan: necessity of implementing a routine vaccination program | Ozaki, Takao | 2013 | 10.1007/s10156-013-0577-x | Not a systematic review |
| 56 | Consensus: varicella vaccination of healthy children: a challenge for Europe | Rentier, Bernard; Gershon, Anne A | 2004 | 10.1097/01.inf.0000122606.88429.8f | Not a systematic review |
| 57 | Impact of varicella vaccine on varicella-zoster virus dynamics | Schmid, D Scott; Jumaan, Aisha O | 2010 | 10.1128/CMR.00031-09 | Not a systematic review |
| 58 | Pediatric Wells syndrome (eosinophilic cellulitis) after vaccination: A case report and review of the literature | Yu, A. M.; Ito, S.; Leibson, T.; Lavi, S.; Fu, L. W.; Weinstein, M.; Skotnicki, S. M. | 2018 | 10.1111/pde.13532 | Not a systematic review |

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| 59 | Successes and challenges in varicella vaccine | Papaloukas, Orestis; Giannouli, Georgia; Papaevangelou, Vassiliki | 2014 | 10.1177/2051013613515621 | Not a systematic review |
| 60 | Varicella and herpes zoster vaccine development: lessons learned | Warren-Gash, Charlotte; Forbes, Harriet; Breuer, Judith | 2017 | 10.1080/14760584.2017.1394843 | Not a systematic review |
| 61 | Varicella vaccination - the global experience | Wutzler, Peter; Bonanni, Paolo; Burgess, Margaret; Gershon, Anne; Safadi, Marco Aurelio; Casabona, Giacomo | 2017 | 10.1080/14760584.2017.1343669 | Not a systematic review |
| 62 | Chickenpox | Breuer, Judith; Fifer, Helen | 2011 | https://pubmed.ncbi.nlm.nih.gov/21486500/ | Not a systematic review |
| 63 | Varicella-zoster virus: pathogenesis, incidence patterns and vaccination programs | Gabutti, Giovanni; Franchi, Michele; Maniscalco, Licia; Stefanati, Armando | 2016 | https://www.minervamedica.it/en/journals/minerva-pediatrics/article.php?cod=R15Y2016N03A0213 | Not a systematic review |
| 64 | Epidemiologic effects of varicella vaccination | Halloran, M Elizabeth | 1996 | 10.1016/S0891-5520(05)70318-4 | Not a systematic review |
| 65 | NACI Statement on measles-mumps-rubella-varicella vaccine - September 2010 | Immunization, National Advisory Committee on | 2010 | https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2010-36/canada-communicable-disease-report-14.html | Not a systematic review |
| 66 | Severe varicella in persons vaccinated with varicella vaccine (breakthrough varicella): a systematic literature review | Leung, J.; Broder, K. R.; Marin, M. | 2017 | 10.1080/14760584.2017.1294069 | Not a systematic review |
| 67 | Vaccine schedules and procedures, 2007 | Middleton, D. B.; Zimmerman, R. K.; Mitchell, K. B. | 2007 | https://pubmed.ncbi.nlm.nih.gov/17270110/ | Not a systematic review |
| 68 | Immunizations, neonatal jaundice and animal-induced injuries | Post, J. N. | 2006 | 10.1097/01.mop.0000193315.52957.e3 | Not a systematic review |
| 69 | Effectiveness of live varicella vaccine | Takahashi, Michiaki | 2004 | 10.1517/14712598.4.2.199 | Not a systematic review |
| 70 | Varicella zoster virus infections in children after the introduction of live attenuated varicella vaccine | Vazquez, Marietta | 2004 | 10.1097/00008480-200402000-00015 | Not a systematic review |
| 71 | Routine vaccines across the life span, 2007 | Zimmerman, R. K.; Middleton, D. B.; Burns, I. T.; Clover, R. D.; Kimmel, S. R. | 2007 | https://pubmed.ncbi.nlm.nih.gov/17270108/ | Not a systematic review |
| 72 | Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States | Halloran, M. E.; Cochi, S. L.; Lieu, T. A.; Wharton, M.; Fehrs, L. | 1994 | 10.1093/oxfordjournals.aje.a117238 | Not a systematic review |
| 73 | International Consensus (ICON): Allergic reactions to vaccines | Dreskin, S. C.; Halsey, N. A.; Kelso, J. M.; Wood, R. A.; Hummell, D. S.; Edwards, K. M.; Caubet, J. C.; Engler, R. J. M.; Gold, M. S.; Ponvert, C.; Demoly, P.; Sanchez-Borges, M.; Muraro, A.; Li, J. T.; Rottem, M.; Rosenwasser, L. J. | 2016 | 10.1186/s40413-016-0120-5 | Not a systematic review |

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| 74 | Trends in varicella epidemiology before and after the implementation of universal one-dose varicella vaccination | Lai, S. W. | 2019 | 10.1080/21645515.2019.1633879 | Not a systematic review |
| 75 | Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004-2009 | Williams, S. E.; Klein, N. P.; Halsey, N.; Dekker, C. L.; Baxter, R. P.; Marchant, C. D.; LaRussa, P. S.; Sparks, R. C.; Tokars, J. I.; Pahud, B. A.; Aukes, L.; Jakob, K.; Coronel, S.; Choi, H.; Slade, B. A.; Edwards, K. M. | 2011 | 10.1016/j.vaccine.2011.07.044 | Not a systematic review |
| 76 | The current status of live attenuated varicella vaccine | Gershon, AA | 2001 | 10.1007/978-3-7091-6259-0_1 | Not a systematic review |
| 77 | Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines | Schattner, Ami | 2005 | 10.1016/j.vaccine.2005.03.005 | Not a systematic review |
| 78 | [Varicella disease and varicella vaccine. A literature review] | Frederiksen, Marianne Sjolin; Plesner, Anne-Marie; Stellfeld, Michael | 2003 | https://pubmed.ncbi.nlm.nih.gov/12840997/ | Not a systematic review |
| 79 | The impact of varicella vaccination on varicella-related hospitalization rates: global data review | Hirose, M.; Gilio, A. E.; Ferronato, A. E.; Ragazzi, S. L. B. | 2016 | 10.1016/j.rppede.2016.03.001 | Not a systematic review |
| 80 | A review of varicella vaccine and Louisiana vaccination requirements | Buff, Ann M.; Welch, Frank J.; Tapia, Ruben A. | 2004 | https://pubmed.ncbi.nlm.nih.gov/15000215/ | Not a systematic review |
| 81 | JCVI Statement on varicella and herpes zoster vaccines - 29 March 2010 | JCVI | 2010 | https://webarchive.nationalarchives.gov.uk/ukgwa/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf | Not a systematic review |
| 82 | Prevention of Varicella | ACIP | 2007 | https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm | Not a systematic review |
| 83 | Impact of routine pediatric varicella vaccination on the epidemiology of herpes zoster | Alain, S.; Paccalin, M.; Larnaudie, S.; Perreaux, F.; Launay, O. | 2009 | 10.1016/j.medmal.2009.04.009 | Not a systematic review |
| 84 | Clinical trials of varicella vaccine in healthy children | White, C Jo | 1996 | 10.1016/S0891-5520(05)70315-9 | Not a systematic review |
| 85 | Primary versus secondary failure after varicella vaccination: Implications for interval between 2 doses | Bonanni, P.; Gershon, A.; Gershon, M.; Kulcsar, A.; Papaevangelou, V.; Rentier, B.; Sadzot-Delvaux, C.; Usonis, V.; Vesikari, T.; Weil-Olivier, C.; De Winter, P.; Wutzler, P. | 2013 | 10.1097/INF.0b013e31828b7def | Not a systematic review |
| 86 | Recommendations for immunization against varicella | Berthet F, Biver A | 2009 | https://sante.public.lu/dam-assets/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/varicelle/2009-vaccination.pdf | Not a systematic review |

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| 87 | Vaccinating children, adolescents and at-risk individuals against varicella | Conseil Supérieur de la Santé, Belgium | 2017 | https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/css_avis_9212_varicelle_veerle_a5.pdf | Not a systematic review |
| 88 | Vaccinating children against varicella: are two doses of vaccine necessary? | Ucakar, Veronika; Socan, Maja | 2012 | doi:10.2478/v10152-012-0023-z | Not a systematic review |
| 89 | Vaccination against chicken pox. Up-date and new authorized indications in Spain | Barrio Corrales, F. | 2004 | https://www.seinap.es/wp-content/uploads/Revista-de-Pediatria/2004/REP%2060-4.pdf | Not a systematic review |
| 90 | Varicella epidemiology in Latin America and the Caribbean | Ãvila-Aguero, M. L.; Beltran, S.; Castillo, J. B. D.; Castillo Diaz, M. E.; Chaparro, L. E.; Deseda, C.; Debbag, R.; Espinal, C.; Falleiros-Arlant, L. H.; Gonzalez Mata, A. J.; Macias Parra, M.; Marques-Rosa, F.; Catalina Pirez, M.; Vazquez-Rivera, M. | 2018 | 10.1080/14760584.2018.1418327 | Not a systematic review |
| 91 | Varicella-zoster virus: aspects of pathogenesis and host response to natural infection and varicella vaccine | Arvin, Ann M; Moffat, Jennifer F; Redman, Rebecca | 1996 | 10.1016/S0065-3527(08)60074-3 | Not a systematic review |
| 92 | Literature Review on One-Dose and Two-Dose Varicella Vaccination | Campbell, A ; Ismail, S ; Tan, B | 2010 | 10.14745/ccdr.v36i00a10 | Not a systematic review |
| 93 | Varicella prevention in the United States: A review of successes and challenges | Marin, M.; Meissner, H. C.; Seward, J. F. | 2008 | 10.1542/peds.2008-0567 | Not a systematic review |
| 94 | Varicella vaccine effectiveness in the US vaccination program: a review | Seward, J. F.; Marin, M.; Vazquez, M. | 2008 | 10.1086/522145 | Not a systematic review |
| 95 | Preventive effectiveness of varicella vaccine in healthy unexposed patients | Castro, Maria Catalina; Rojas, Pamela | 2020 | 10.5867/medwave.2020.06.7982 | Not a systematic review |
| 96 | [Varicella: clinical aspects and prevention] | Carvalho, E. S.; Martins, R. M. | 1999 | 10.2223/jped.379 | Not a systematic review |
| 97 | Chickenpox | Swingler, George H. | 2007 | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2943770/ | Not a systematic review |
| 98 | The state of vaccine safety science: systematic reviews of the evidence | Dudley, M. Z.; Halsey, N. A.; Omer, S. B.; Orenstein, W. A.; O'Leary, S. T.; Limaye, R. J.; Salmon, D. A. | 2020 | 10.1016/S1473-3099(20)30130-4 | Not a systematic review |
| 99 | NACI Varicella Vaccination Two-Dose Recommendations | NACI | 2010 | https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2010-36/canada-communicable-disease-report-1.html | Not a systematic review |
| 100 | Varicella vaccination two-dose recommendations. National Advisory Committee on Immunization (NACI) | Tan, B., Ismail, S. | 2010 | 10.14745/ccdr.v36i00a08 | Not a systematic review |

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|---|---|---|---|---|---|
| 101 | Varicella and herpes zoster vaccines | WHO | 2014 | https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/varicella/who-pp-varicella-herpes-zoster-june2014-references.pdf?sfvrsn=31c10d0a_2 | Not a systematic review |
| 102 | Modified chickenpox in children immunized with the Oka/Merck varicella vaccine | Watson, Barbara M; Piercy, Sharon A; Plotkin, Stanley A; Starr, Stuart E | 1993 | https://pubmed.ncbi.nlm.nih.gov/8416499/ | Not a systematic review |
| 103 | Keratitis in association with herpes zoster and varicella vaccines | Grillo, A. P.; Fraunfelder, F. W. | 2017 | 10.1358/dot.2017.53.7.2667582 | Not a systematic review |
| 104 | A new combination vaccine for measles, mumps, rubella and varicella | Zareba, G. | 2006 | 10.1358/dot.2006.42.5.973586 | Not a systematic review |
| 105 | Immunoprophylaxis of chickenpox and shingles | Petkova, T.; Doychinova, Tz | 2016 | https://www.researchgate.net/publication/316666392_Immunoprophylaxis_of_chickenpox_and_shingles | Not a systematic review |
| 106 | Safety of Vaccines Used for Routine Immunization in the United States | Maglione, Margaret A.; Gidengil, Courtney; Das, Lopamudra; Raaen, Laura; Smith, Alexandria; Chari, Ramya; Newberry, Sydne; Hempel, Susanne; Shanman, Roberta; Perry, Tanja; Goetz, Matthew Bidwell | 2014 | 10.23970/AHRQEPCERTA215 | Review has been updated |
| 107 | Safety of vaccines used for routine immunization of US children: A systematic review | Maglione, M. A.; Das, L.; Raaen, L.; Smith, A.; Chari, R.; Newberry, S.; Shanman, R.; Perry, T.; Goetz, M. B.; Gidengil, C. | 2014 | 10.1542/peds.2014-1079 | Review has been updated |
| 108 | Use of varicella vaccine in healthy populations: systematic review and recommendations | Skull, S. A.; Wang, E. E. L.; with the Canadian Task Force on Preventive Health, Care | 2000 | https://canadiantaskforce.ca/wp-content/uploads/2016/09/2001-varicella-vaccine-systematic-review-and-recommendations-en.pdf | Review has been updated |
| 109 | Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: a meta-analysis of randomized controlled trials | Leung, Julia Hy; Hirai, Hoyee W.; Tsoi, Kelvin Kf | 2015 | 10.1586/14760584.2015.1057572 | Wrong comparator |
| 110 | Meta analysis on the safety and immunogenicity of domestic varicella vaccine among Chinese population. [Chinese] | Li, LanXin, He, Jia | 2013 | https://caod.oriprobe.com/articles/37711085/guo_chan_shui_dou_jian_du_huo_yi_miao_zai_zhong_gu.htm | Wrong comparator |
| 111 | Immunogenicity and safety of measles-mumps-rubella-varicella vaccine: A systematic review | Wu, Y. M.; Li, G.; Zhao, W. L. | 2010 | http://caod.oriprobe.com/articles/24297599/Immunogenicity_and_Safety_of_Measles_Mumps_Rubella_Varicella_Vaccine__.htm | Wrong comparator |
| 112 | Metaanalysis of vaccine effectiveness in varicella outbreaks | Bayer, O; Heininger, U; Heiligensetzer, C; von Kries, R | 2007 | 10.1016/j.vaccine.2007.07.010 | Wrong outcome |

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|---|---|---|---|---|---|
| 113 | Global Varicella Vaccine Effectiveness: A Meta-analysis | Marin, Mona; Marti, Melanie; Kambhampati, Anita; Jeram, Stanley M;Seward, Jane F. | 2016 | 10.1542/peds.2015-3741 | Wrong outcome |
| 114 | Incidence rate of breakthrough varicella observed in healthy children after 1 or 2 doses of varicella vaccine: Results from a meta-analysis | Zhu, Sui; Zeng, Fangfang; Xia, Lan; He, Hong; Zhang, Juying | 2018 | 10.1016/j.ajic.2017.07.029 | Wrong outcome |
| 115 | Two-dose varicella vaccine effectiveness in China: a meta-analysis and evidence quality assessment | Zhang, Zhujiazi; Suo, Luodan; Pan, Jingbin; Zhao, Dan; Lu, Li | 2021 | 10.1186/s12879-021-06217-1 | Wrong outcome |
| 116 | Systematic reviews and evidence quality assessment on effectiveness of 1 dose varicella attenuated live vaccine for healthy children aged 1-12 years in China | Zhang, Z. J. Z; Suo, L. D; Zhao, D; Pan, J. B; Lu, L. | 2020 | 10.3760/cma.j.cn112338-20191025-00762 | Wrong outcome |
| 117 | Meta-analysis of documents on vaccine effectiveness of live attenuated varicella vaccine in pupils and preschoolers | Xu, A. Y; Pang, H. | 2019 | http://www.cqvip.com/qk/97789x/20195/7002176336.html | Wrong outcome |
| 118 | The clinical and economic burden of varicella in the Middle East: a systematic literature review | Al Kaabi, Nawal; Al Olama, Fatma Mohd Ali Sultan; Al Qaseer, Mamoun; Al Ubaidani, Idris; Dinleyici, Ener Cagri; Hayajneh, Wail Ahmad; Bizri, Abdul Rahman; Loulou, Maysoon; Ndao, Tidiane; Wolfson, Lara J. | 2020 | 10.1080/21645515.2019.1638726 | Wrong outcome |
| 119 | Burden of varicella in Latin America and the Caribbean: findings from a systematic literature review | Arlant, Luiza Helena Falleiros; Garcia, Maria Catalina Pirez; Avila Aguero, Maria L; Cashat, Miguel; Parellada, Cintia Irene; Wolfson, Lara J. | 2019 | 10.1186/s12889-019-6795-0 | Wrong outcome |
| 120 | Burden of varicella in the Asia-Pacific region: a systematic literature review | Goh, Anne Eng Neo; Choi, Eun Hwa; Chokephaibulkit, Kulkanya; Choudhury, Jaydeep; Kuter, Barbara; Lee, Ping-Ing; Marshall, Helen; Kim, Jin Oh; Wolfson, Lara J. | 2020 | 10.1080/14760584.2019.1594781 | Wrong outcome |
| 121 | Burden of varicella in Central and Eastern Europe: findings from a systematic literature review | Mészner, Zsófia; Wysocki, Jacek; Richter, Darko; Zavadska, Dace; Ivaskeviciene, Inga; Usonis, Vytautas; Pokorn, Marko; Mangarov, Atanas; Jancoriene, Ligita; Man, Sorin C; Kristufkova, Zuzana; Jesenak, Milos; Tešović, Goran; Pluta, Justyna; Wolfson, Lara J. | 2020 | 10.1080/14760584.2019.1573145 | Wrong outcome |
| 122 | Varicella vaccination in Italy and Germany–different routes to success: a systematic review | Kauffmann, F; Bechini, A; Bonanni, P; Casabona, G; Wutzler, P. | 2020 | 10.1080/14760584.2020.1825947 | Wrong outcome |

## Appendix A6.1 Search strategies

| | |
|---|---|
| **Database Name** | Embase (Ovid) |
| **Date search was run** | 28/06/2022 |

Database(s): **Embase** 1974 to 2022 June 27

| # | Searches | Results |
|---|---|---|
| 1 | (chickenpox or 'chicken pox' or varicella or 'varicella-zoster virus').ab,ti. | 21285 |
| 2 | exp chickenpox/ | 12287 |
| 3 | 1 or 2 | 25037 |
| 4 | (vaccin* or immuni* or inocula*).ab,ti. | 843568 |
| 5 | (varilrix or varivax or 'priorix tetra' or proquad or mmrv).ab,ti. | 416 |
| 6 | exp chickenpox vaccine/ | 5173 |
| 7 | exp vaccination/ | 206272 |
| 8 | exp immunization/ | 329986 |
| 9 | exp chickenpox measles mumps rubella vaccine/ or chickenpox/ | 12520 |
| 10 | 4 or 5 or 6 or 7 or 8 or 9 | 918241 |
| 11 | Economics/ | 243685 |
| 12 | Cost/ | 60967 |
| 13 | exp Health Economics/ | 962222 |
| 14 | Budget/ | 31719 |
| 15 | budget*.ti,ab,kf. | 44512 |
| 16 | (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. | 322016 |
| 17 | (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 | 484009 |
| 18 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. | 267797 |
| 19 | (value adj2 (money or monetary)).ti,ab,kf. | 3780 |
| 20 | Statistical Model/ | 170518 |
| 21 | economic model*.ab,kf. | 5741 |
| 22 | Probability/ | 129751 |
| 23 | markov.ti,ab,kf. | 34899 |
| 24 | monte carlo method/ | 46494 |
| 25 | monte carlo.ti,ab,kf. | 58221 |
| 26 | Decision Theory/ | 1809 |
| 27 | Decision Tree/ | 17662 |
| 28 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. | 44255 |
| 29 | or/11-28 | 1864933 |
| 30 | 3 and 10 and 29 | 1460 |
| 31 | limit 30 to yr="2013 -Current" | 532 |

| | |
|---|---|
| **Database Name** | Medline (EBSCO) |
| **Date search was run** | 28/06/2022 |

| # | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S11 | S3 AND S8 AND S9 | Limiters - Date of Publication: 20130101-20221231<br>Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 234 |
| S10 | S3 AND S8 AND S9 | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 609 |
| S9 | 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<br>Search modes - Boolean/Phrase | 1,340,535 |
| S8 | S4 OR S5 OR S6 OR S7 | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 790,993 |

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|---|---|---|---|
| S7 | AB ( varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV ) OR TI ( varilrix OR varivax OR PRIORIX-TETRA OR proquad OR MMRV ) | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 305 |
| S6 | (MH "Chickenpox Vaccine+") | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 3,156 |
| S5 | (MH "Vaccination+") OR (MH "Immunization+") | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 197,721 |
| S4 | AB ( vaccin* OR immuni* OR inocula* ) OR TI ( vaccin* OR immuni* OR inocula* ) | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 734,433 |
| S3 | S1 OR S2 | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 18,353 |
| S2 | (MH "Chickenpox") | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 7,754 |
| S1 | AB ( Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus" ) OR TI ( Chicken pox OR chickenpox OR varicella OR "varicella-zoster virus" ) | Expanders - Apply equivalent subjects<br>Search modes - Boolean/Phrase | 17,180 |

# Appendix A6.2 Data Extraction Tables

| | | | |
|---|---|---|---|
| **General study characteristics** | **Author Name, Year of Publication, DOI** | Akpo et al. 2020[132] DOI: 10.1093/cid/ciaa1708 | |
| | **Region, Country** | UK | |
| | **Type of Economic Evaluation** | CUA and CBA | |
| | **Population** | Stationary population (demographic changes not modelled) | |
| | **Funding** | Industry (GSK) | |
| **Model characteristics** | **Model type** | Population level age-structured dynamic transmission model<br>Note: Contact pattern data were obtained from the POLYMOD study.[135] | |
| | **Perspective** | 1. Societal<br>2. Health care payer | |
| | **Time horizon** | 20yrs (short-term), 40yrs (medium-term), 100yrs (long-term) | |
| | **Comparator** | No vaccination | |
| | **Discount rates** | 3.5% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | 1st dose monovalent (mono)/quadrivalent (quad) MMRV; 2nd dose quadrivalent MMRV | |
| | **Age at vaccination** | mono + quad: 1st dose mono at 13mths; 2nd dose quad at 3yrs 4mths<br>quad + quad: 1st dose quad at 12mths; 2nd dose quad at 3yrs 4mths | |
| | **Coverage rate** | mono + quad: 87% for 1st dose and 2nd dose<br>quad + quad: 95% for 1st dose and 87% for 2nd dose (coverage assumed the same as current MMR rates) | |
| **Model input parameters** | **Efficacy/effectiveness** | Efficacy (GSK vaccines): 1-dose: 67.2%; 2-dose 95.4%<br>Efficacy (MSD vaccines): 1-dose: 78%; 2-dose 98.3% | |
| | **Waning** | 1st dose 30yrs; 2nd dose permanent (progressive immunity) | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ GP visits (varicella, BV, wildtype and breakthrough HZ)<br>▪ Hospitalisation (varicella, BV, wildtype and breakthrough HZ)<br>▪ Vaccine<br>▪ Vaccine administration<br>▪ Extra time for monovalent vaccine<br>▪ GP visits (related to vaccine adverse events except febrile seizures)<br>▪ Emergency rooms visits (related to febrile seizures)<br><br>**Indirect costs**<br>▪ Productivity loss associated with varicella, BV and HZ | **Measurement and valuation**<br>**Direct costs**<br>▪ % of varicella cases with GP visits, number of visits per case, cost per visit (including treatment cost) for varicella<br>▪ Relative propensity (compared to wildtype) for breakthrough varicella to consult GP, number of GP visits per breakthrough varicella case, cost per visit (including treatment cost) for varicella<br>▪ % of HZ cases with GP visits, number of visits per case, cost per visit for HZ<br>▪ Relative propensity (compared to wildtype) for breakthrough HZ to consult GP<br>▪ Cost for medication and GP visit for PHN<br>▪ % of varicella cases hospitalised, hospital length of stay for varicella, cost of hospitalisation day for varicella<br>▪ Relative propensity (compared to wildtype) for breakthrough hospitalised varicella<br>▪ % of HZ cases hospitalised, hospital length of stay for HZ, cost of hospitalisation day for HZ<br>▪ Relative propensity (compared to wildtype) for breakthrough hospitalised HZ<br><br>▪ Price per vaccine dose<br>▪ Cost of vaccine administration<br>▪ Cost of extra time for monovalent vaccine<br>▪ Injection site adverse events (%) and risk of febrile seizure<br>▪ % with GP visit following vaccine adverse reaction (except febrile seizure) and cost per visit |

| | | | |
|---|---|---|---|
| | | | ▪ % with ER visit following vaccine adverse reaction (only febrile seizure) and cost per visit (1 overnight stay)<br><br>**Indirect costs**<br>▪ Number of days off work secondary to varicella, BV and HZ<br>▪ Mean income |
| | **Effects included** | **<u>Type of Effects</u>**<br>**Direct effects**<br>▪ Incidence of varicella and BV<br>▪ Incidence of HZ (wildtype and breakthrough) with and without PHN (by age)<br>▪ Age at varicella and HZ infection<br><br>**Indirect effects**<br>▪ Incidence of HZ (exogenous boosting) | **<u>Measurement and valuation</u>**<br><br>**Indirect effects**<br>▪ % of effective varicella contacts that boost against HZ by age (0-49yrs, 50-69yrs, 70-79yrs, 80+yrs)<br>▪ Duration of boosting (2yrs) against HZ based on calibration<br><br>**QALY loss per case**<br>▪ Varicella by age (0-14yrs and 15yrs+)<br>▪ BV<br>▪ HZ or breakthrough HZ without PHN by age (0-14yrs, 15-44yrs, 45-64yrs, 65+yrs)<br>▪ HZ or breakthrough HZ with PHN by age (0-14yrs, 15-44yrs, 45-64yrs, 65+yrs) |
| **Economic results** | **Type of summary ratio** | ICUR (Incremental cost/QALY gained) | |
| | **Overall payer perspective result** | The mono+quad strategy (for both vaccines) was cost-effective across all time horizons with ICURs <£20,000/QALY gained.<br>The quad+quad strategy was cost-effective in the medium (GSK only) and long-term only with ICURs <£20,000/QALY gained. | |
| | **Overall societal perspective result** | The mono+quad strategy (for both vaccines) was cost-effective across all time horizons with ICURs <£20,000/QALY gained (GSK vaccine was dominant in the long-term).<br>The quad+quad strategy was cost-effective across all time horizons with ICURs <£20,000/QALY gained. | |
| **Authors conclusions** | A 2-dose UVV was demonstrated to be a cost-effective alternative to no vaccination. | | |

**Key:** BV – breakthrough varicella; CBA – cost-benefit analysis; CUA – cost utility analysis; HZ – herpes zoster; ICUR – incremental cost utility ratio; MMRV – measles, mumps, rubella, varicella; PHN – post herpetic neuralgia; QALY – quality adjusted life year;

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|---|---|---|---|
| **General study characteristics** | **Author Name, Year of Publication, DOI** | Azzari et al. 2020[133] DOI: 10.2147/CEOR.S229685 | |
| | **Region, Country** | Italy | |
| | **Type of Economic Evaluation** | CEA | |
| | **Population** | Population of Italy segmented by age | |
| | **Funding** | Industry (Merck) | |
| **Model characteristics** | **Model type** | Population level, age-structured, deterministic dynamic transmission model<br>Note: Model used a MSEIRS structure (Maternal/Passive Immunity-Susceptible-Exposed-Infectious-Recovered-Susceptible).<br>Model segmented into seven age groups (<1yrs, 1-4yrs, 5-9yrs, 10-14yrs, 15-44yrs, 45-64yrs, ≥65yrs).<br>Contact pattern data were derived assuming proportionate mixing, that is, mixing between age groups is proportional to their activity level.<br>To simulate different vaccination strategies in the Italian population, age-specific contact rates and seroprevalence needed to be calibrated for the dynamic transmission model based on Italian annual population data, Italian annual fertility data and measured pre-vaccine era seroprevalence. | |
| | **Perspective** | 1. Societal<br>2. Health care payer | |
| | **Time horizon** | 50yrs | |
| | **Comparator** | Strategies below in comparison to each other and no vaccination | |
| | **Discount rates** | 3.0% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | 1st dose quadrivalent MMRV; 2nd dose quadrivalent MMRV (Strategies A and B using both MSD and GSK vaccines exclusively)<br>1st dose monovalent; 2nd dose quadrivalent MMRV (Strategies C and D strategies using both MSD and GSK vaccines exclusively) | |
| | **Age at vaccination** | 1st dose mono/quad at 13-15mths; 2nd dose quad at 5-6yrs | |
| | **Coverage rate** | 1st dose mono 81%; 1st dose quad 85%<br>2nd dose quad: 83% | |
| **Model input parameters** | **Efficacy/effectiveness** | Efficacy MSD ProQuad® vaccine: 1-dose 100%; 2-dose 100%<br>Efficacy GSK Priorix-Tetra® vaccine: 1-dose 65.4%; 2-dose 94.9%<br>Strategy A: 1-dose 100%; 2-dose 100%<br>Strategy B: 1-dose 100%; 2-dose 100%<br>Strategy C: 1-dose 75%; 2-dose 95%<br>Strategy A: 1-dose 75%; 2-dose 95% | |
| | **Waning** | MSD ProQuad® vaccine: 1-dose 4% p.a. (1/25yrs); 2-dose 1.3% p.a. (1/77yrs)<br>GSK Priorix-Tetra® vaccine: 1st dose 5.88% p.a. (1/17yrs); 2-dose lifetime immunity<br>Strategy A: 1-dose 4% p.a.; 2-dose 1.3% p.a.<br>Strategy B: 1-dose 4% p.a.; 2-dose 1.3% p.a.<br>Strategy C: 1-dose 6.7% p.a.; 2-dose 2% p.a.<br>Strategy D: 1-dose 6.7% p.a.; 2-dose 2% p.a. | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ Outpatient visits (varicella)<br>▪ Hospitalisation (varicella)<br>▪ Prescription and OTC drugs per inpatient and outpatient<br>▪ Diagnostic tests per inpatient and outpatient<br>▪ Vaccines<br>▪ Delivery, cold-chain and administration of monovalent vaccine<br>▪ Febrile seizures associated with quadrivalent vaccine<br><br>**Indirect costs**<br>▪ Productivity loss associated with varicella for outpatients and inpatients (ages 15 to 64yrs only)<br>▪ Productivity loss for caregivers of outpatients (cases aged <15yrs)<br>▪ Productivity loss for caregivers of inpatients (cases aged | **Measurement and valuation**<br>**Direct costs**<br>▪ % of cases requiring an outpatient visit and cost per visit<br>▪ % of varicella cases hospitalised, number of days per hospitalisation and cost per day<br>▪ Total cost of prescription/OTC drugs per inpatient and outpatient<br>▪ Total cost of diagnostic tests per inpatient and outpatient<br>▪ Cost of vaccines estimated as 50% of the net maximum selling price<br>▪ Total cost of administration, delivery and cold storage<br>▪ Cost of febrile seizure per vaccinated person based on cost of a hospitalised case and rate of additional febrile seizures with quad compared with mono vaccine<br><br>**Indirect costs**<br>▪ Days of work lost and average cost per workday missed |

| | | | |
|---|---|---|---|
| | | <15yrs) | |
| | **Effects included** | **<u>Type of Effects</u>**<br>**Direct effects**<br>▪ Incidence of varicella<br>▪ Hospitalised cases<br>▪ Death<br>▪ Incidence of HZ<br><br>**Indirect Effects**<br>▪ NR | **<u>Measurement and valuation</u>**<br>**Direct effects**<br>▪ NR<br><br>**QALY loss per case**<br>▪ Varicella and BV<br>▪ HZ and breakthrough HZ<br>▪ PHN |
| **Economic results** | **Type of summary ratio** | ICER | |
| | **Overall payer perspective result** | All four strategies dominate no vaccination with 2-dose quad (MSD) the least costly and most effective | |
| | **Overall societal perspective result** | All four strategies dominate no vaccination with 2-dose quad (MSD) the least costly and most effective | |
| **Authors conclusions** | The model predicts that various two-dose vaccination strategies are cost-saving compared to no vaccination.<br>2-dose quadrivalent MMRV (MSD) vaccination offers the greatest benefits at the lowest cost and should be considered as a potential priority strategy for the Italian population. | | |

**Key:** BV - breakthrough varicella; CEA - cost effectiveness analysis; HZ - herpes zoster; ICER - incremental cost effectiveness ratio; MMRV - measles, mumps, rubella, varicella; NR - not reported; PHN - post herpetic neuralgia; QALY - quality adjusted life year;

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|---|---|---|---|
| **General study characteristics** | **Author Name, Year of Publication, DOI** | Heininger et al. 2021[131] DOI: 10.1097/INF.0000000000003136 | |
| | **Country** | Switzerland | |
| | **Type of Economic Evaluation** | CUA | |
| | **Population** | NR | |
| | **Funding** | Industry (Merck) | |
| **Model characteristics** | **Model type** | Age-structured deterministic dynamic transmission model<br>Note: Model adapted from other studies including that used in Azarri et al. 2020 (Italy)[133] and used a static population size and age distribution.<br>Contact pattern data were projected from POLYMOD data.[135]<br>Model calibration was achieved using the output from the force of mortality calculation and several sources of data on pre-vaccination varicella prevalence in Switzerland. | |
| | **Perspective** | 1. Societal<br>2. Health care payer | |
| | **Time horizon** | Base case 50yrs (also considered 25yrs and 100yrs) | |
| | **Comparator(s)** | 1. No vaccination<br>2. 10% private market coverage of 2-dose MMRV at 9mths and 12mths | |
| | **Discount rates** | 3% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | 1st dose: quadrivalent MMRV; 2nd dose quadrivalent MMRV or monovalent | |
| | **Age at vaccination** | Strategy 1: 1st dose at 9mths (MMRV), 2nd dose at 12mths (MMRV);<br>Strategy 2: 1st dose at 12mths (MMRV), 2nd dose at 19mths (MMRV);<br>Strategy 3: 1st dose at 9mths (MMRV), 2nd dose at 24mths (varicella only); | |
| | **Coverage rate** | 95% for 1st dose; 90% for 2nd dose | |
| **Model input parameters** | **Efficacy/effectiveness** | NR | |
| | **Waning** | NR | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ Inpatient and outpatient visits<br>▪ Treatments<br>▪ Diagnostics<br>▪ Hospitalisation<br>▪ Vaccine<br>▪ Administration, delivery and cold-chain requirements for varicella only vaccine (assumed MMRV vaccine given instead of current MMR vaccine and therefore no additional cost)<br>▪ Febrile seizure (MMRV vaccine)<br>▪ Treatment for HZ (uncomplicated and complicated with PHN)<br><br>**Indirect costs**<br>▪ Productivity loss for those ill with varicella<br>▪ Productivity loss for carers of those with varicella<br>▪ Productivity loss for those ill with HZ | **Measurement and valuation**<br>**Direct costs**<br>▪ % of cases requiring outpatient visits, number of outpatient visits per case (all by age) and cost per outpatient visit<br>▪ % of cases requiring hospitalisation, mean duration of hospital stay and mean cost per hospital day (all by age)<br>▪ % of outpatient cases requiring prescription or OTC medication and mean cost of each for outpatients (all by age)<br>▪ % of cases requiring diagnostic test and mean cost of diagnostic test per case<br>▪ Incidence of HZ, % of HZ cases that develop PHN and mean cost per case of HZ (uncomplicated and complicated with PHN) (all by age)<br><br>**Indirect costs**<br>▪ Mean days lost from work (outpatient and inpatient) (by age) and mean cost per work day missed for productivity losses<br>▪ Febrile seizure – number of cases per dose and cost per case |
| | **Effects included** | **Type of Effects**<br>**Direct effects**<br>▪ Cases of varicella<br>▪ Hospitalisations<br>▪ Deaths<br>▪ Herpes zoster<br><br>**Indirect effects**<br>▪ NR | **Measurement and valuation**<br><br>**QALY loss per case**<br>▪ Reported per case for each vaccination strategy but not for each health effect |

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| **Economic results** | **Type of summary ratio** | ICER (Incremental cost/QALY gained) |
| | **Overall payer perspective result** (no formal cost-effectiveness thresholds defined in Switzerland) | The ICERs for UVV compared with no infant vaccination vary from CHF31,194 to CHF34,793/QALY gained (likely to be cost-effective).† The ICERs for UVV compared with 10% private infant vaccination vary from CHF31,357 to CHF35,403/QALY gained (likely to be cost-effective).† |
| | **Overall societal perspective result** (no formal cost-effectiveness thresholds defined in Switzerland | The ICERs for UVV compared with no infant vaccination vary from CHF25,245 to CHF28,762/QALY gained (likely to be cost-effective).† The ICERs for UVV compared with 10% private infant vaccination vary from CHF25,559 to CHF29,552/QALY gained (likely to be cost-effective).† |
| **Authors conclusions** | UVV appears highly effective and cost-effective when compared with current clinical practice and recommendations in Switzerland from both a direct medical cost perspective and societal perspective. | |

†There are no formal cost-effectiveness thresholds defined in Switzerland.
**Key:** BV – breakthrough varicella; CUA – cost utility analysis; HZ – herpes zoster; MMRV – measles, mumps, rubella, varicella; PHN – post herpetic neuralgia; QALY – quality adjusted life year; UVV – universal varicella vaccination

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| **General study characteristics** | **Author Name, Year of Publication, DOI** | Littlewood et al. 2015[127] DOI: 10.1016/j.clinthera.2015.01.006 0149-2918/$ | |
| | **Region, Country** | France | |
| | **Type of Economic Evaluation** | CEA | |
| | **Population** | Population of France | |
| | **Funding** | Industry (GSK) | |
| **Model characteristics** | **Model type** | Age-structured dynamic transmission model using empirical based contact matrix.<br>Note: No empirical French data were available for the contact matrix, so Italian POLYMOD data were used.[135]<br>Details of the dynamic model (including calibration and validation), the impact of the contact matrix, and exogenous boosting on varicella and zoster disease epidemiology have been reported separately by Ouwens et al. | |
| | **Perspective** | 1. Societal<br>2. Health care payer | |
| | **Time horizon** | 80yrs | |
| | **Comparator** | No vaccination | |
| | **Discount rates** | 4.0% for costs and outcomes until 30yrs after vaccination; 2% for costs and outcomes from 30yrs after vaccination | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | Quadrivalent MMRV (model assumes MMRV will replace MMR within 3yrs) + monovalent for catch-up programme | |
| | **Age at vaccination** | 1st dose at 12mths; 2nd dose at 18mths + catch-up programme (to run for 8yrs) for children aged 10yrs | |
| | **Coverage rate** | 1st dose: 90%; 2nd dose: 80% (French MMR coverage rates) | |
| **Model input parameters** | **Efficacy/effectiveness** | Efficacy: 2-dose 95% | |
| | **Waning** | Duration of protection: 17yrs after the 1st dose; lifelong after 2nd dose for those successfully vaccinated (i.e., fully protected) | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ GP/outpatient/home visits (varicella and HZ)<br>▪ Medication (varicella and HZ)<br>▪ Additional examinations (varicella)<br>▪ Laboratory tests (HZ)<br>▪ Hospitalisation (varicella and HZ)<br>▪ Vaccine (varicella)<br>▪ Adverse events associated with vaccine (febrile seizures)<br><br>**Indirect costs**<br>▪ Workdays lost for parents of children with varicella<br>▪ Alternative childcare arrangements<br>▪ Workdays lost for adults patients with varicella and HZ | **Measurement and valuation**<br>**Direct costs**<br>▪ % of cases requiring a GP/outpatient visit, cost per patient by age for varicella and cost per patient (all ages) with/without PHN for HZ<br>▪ Weighted average of hospital costs per case (including all complications) for varicella and HZ<br>▪ Cost per dose of vaccine<br>▪ % with febrile seizure after vaccine and hospitalised cost per case<br><br>**Indirect costs**<br>▪ Varicella - % whose parents lost work time, workdays lost per case, % with alternative childcare costs (age <18yrs)<br>▪ Varicella - % who lost work time, workdays lost per case, % of breakthrough cases with indirect costs (age 18-65yrs)<br>▪ HZ - % who lost work time, workdays lost per case, % of breakthrough cases with indirect costs<br>▪ Cost of alternative childcare<br>▪ Cost per workday lost |
| | **Effects included** | **Type of Effects**<br><br>**Direct effects**<br>▪ Cases of varicella and BV (age-specific)<br>▪ Cases of HZ and breakthrough HZ<br>▪ Hospitalised cases (varicella and BV)<br>▪ Complications (varicella and BV)<br>▪ Death (varicella and BV)<br><br>**Indirect effects**<br>▪ Impact on incidence of HZ (exogenous boosting) | **Measurement and valuation**<br>**Direct effects**<br>▪ % of cases hospitalised (varicella, BV, HZ and breakthrough HZ)<br>▪ Mean number of complications per varicella and zoster case (by age) and relative propensity for breakthrough to cause complications<br>▪ Mean number of deaths per varicella (all ages) and zoster (by age) case and relative propensity for breakthrough to cause death<br><br>**Indirect effects**<br>▪ Age-specific rates of exogenous boosting (<50yrs, 50-64yrs, >65yrs) |

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| | | | **QALY loss per case**<br>▪ Varicella (by age: 0-14yrs; ≥15yrs)<br>▪ BV (all ages)<br>▪ HZ with and without PHN by age (0-59yrs, 60-64yrs, ≥65yrs)<br>▪ Breakthrough HZ (with and without PHN) by age BV (0-59yrs, 60-64yrs, ≥65yrs) |
| **Economic results** | **Type of summary ratio** | ICER (Incremental cost/QALY gained) | |
| | **Overall payer perspective result** | Routine MMRV vaccination cost-effective at 15yrs post implementation with cost/QALY gained <€20,000 | |
| | **Overall societal perspective result** | Routine MMRV vaccination dominant | |
| **Authors conclusions** | The CEA for France suggests that routine MMRV vaccination is expected to provide more QALYs gained, fewer complications, and fewer deaths in the long term compared with MMR (no varicella vaccination), as well as provide significant savings in direct and indirect costs. | | |

**Key:** BV – breakthrough varicella; CEA – cost effectiveness analysis; HZ – herpes zoster; ICER – incremental cost effectiveness ratio; MMRV – measles, mumps, rubella, varicella; PHN – post herpetic neuralgia; QALY – quality adjusted life year;

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| **General study characteristics** | **Author Name, Year of Publication, DOI** | Melegaro et al. 2018[134] DOI: 10.1186/s12916-018-1094-7 | |
| | **Region, Country** | Italy | |
| | **Type of Economic Evaluation** | CUA | |
| | **Population** | Population of Italy | |
| | **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 model (impact of HZ vaccination is also modelled but data extraction relates to varicella vaccination only)<br>Note: Model is informed with historical demographic data and available demographic projections and calibrated on age-specific varicella serological profile and age-specific HZ incidence.<br>The contact matrices were based on a synthetic matrix derived from age specific contact patterns and validated through comparison with POLYMOD results.[135]<br>The calibration of the model was carried out using Monte Carlo Markov chain (MCMC) methods applied to the binomial likelihood of the VZV seroprevalence profile in 1996–1997. Details are provided in the supplementary file. | |
| | **Perspective** | Taxpayer | |
| | **Time horizon** | 25yrs (short), 50yrs (medium) and 85yrs (long-term) | |
| | **Comparator** | No vaccination | |
| | **Discount rates** | 3% and 0% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | NR | |
| | **Age at vaccination** | 1st dose at 15mths; 2nd dose at 5-6yrs | |
| | **Coverage rate** | 80% | |
| **Model input parameters** | **Efficacy/effectiveness** | Efficacy: 1-dose 80%; 2-dose 96% | |
| | **Waning** | NR | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ GP visits (varicella and HZ)<br>▪ Treatment<br>▪ Hospitalisation<br>▪ Vaccine cost<br>▪ Vaccine administration cost<br><br>**Indirect costs**<br>▪ NA | **Measurement and valuation**<br>**Direct costs**<br>▪ Number of GP consultations per varicella case (by age - <14yrs and ≥14yrs) and BV case (all ages), consultation cost and treatment cost per case<br>▪ Hospitalisation rate for varicella, propensity for BV to cause hospitalisation, hospitalisation cost per case of varicella (by age - <14yrs and ≥14yrs)<br>▪ Outpatient cost per case of HZ (incl. visit, treatment and diagnostics)<br>▪ Outpatient cost per case of PHN (incl. visit, treatment and diagnostics)<br>▪ Hospitalisation cost per case of HZ (by age - <49yrs and ≥50yrs)<br>▪ Hospitalisation cost per case of PHN (by age - <49yrs and ≥50yrs)<br>▪ Cost per dose of vaccine<br>▪ Admin cost per dose of vaccine<br><br>**Indirect costs**<br>▪ NA |
| | **Effects included** | **Type of Effects**<br><br>**Direct effects**<br>▪ Averted cases of varicella (incl. BV) and HZ (with and without PHN)<br>▪ Averted deaths<br><br>**Indirect effects**<br>▪ Impact on incidence of HZ (exogenous boosting – progressive | **Measurement and valuation**<br><br>**Indirect effects**<br>▪ Progressive partial immunity - each boosting event progressively reduces the risk of VZV reactivation into HZ. The rate of VZV reactivation decreases with the number of re-exposures to VZV, while it increases with both the time elapsed since the last re-exposure and the individual's age<br>▪ Temporary full immunity - each boosting event provides partial |

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| | | partial immunity [PI] and temporary full immunity [TI]) | complete immunity to HZ.<br><br>**Utilities (varicella only) and QALY loss per case**<br>▪ Varicella (by age: 0-14yrs; ≥15yrs)<br>▪ Reduction in QALY loss for mild versus severe varicella<br>▪ HZ by age (20yrs, 40yrs, 60yrs, 80yrs)<br>▪ PHN by age<br>▪ Death |
| **Economic results** | **Type of summary ratio** | ICER (Incremental cost/QALY gained) | |
| | **Overall taxpayer perspective result** | Assuming temporary complete immunity due to EB, routine varicella vaccination was cost-effective versus no vaccination in the short-term (ICER €2,219/QALY gained) and dominated no vaccination in the medium and long-term scenarios.<br>Assuming progressive partial immunity due to EB, routine varicella vaccination was weakly dominated versus no vaccination in the short-term, strongly dominated in the medium term and was cost-effective in the long-term (€1,517/QALY gained). | |
| **Authors conclusions** | Varicella vaccination would negatively impact the overall burden of VZV in the short and the medium term. Hence, the introduction of a varicella vaccination strategy on its own would not be considered cost-effective from the health care payer perspective. | | |

**Key:** BV – breakthrough varicella; CEA – cost effectiveness analysis; EB – exogenous boosting; HZ – herpes zoster; ICER – incremental cost effectiveness ratio; MMRV – measles, mumps, rubella, varicella; NA – not applicable; PHN – post herpetic neuralgia; QALY – quality adjusted life year; VZV – varicella zoster virus;

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| **General study characteristics** | **Author Name, Year of Publication, DOI** | Pawaskar et al. 2021[129] DOI: 10.1371/journal.pone.0254080 | |
| | **Country** | Norway | |
| | **Type of Economic Evaluation** | CUA | |
| | **Population** | 15mth old children | |
| | **Funding** | Industry (Merck) | |
| **Model characteristics** | **Model type** | Age-structured deterministic dynamic compartmental transmission model<br>Note: Model adapted from elsewhere. Source for contact pattern data not reported.<br>The model employed a static population size and age distribution. Other demographic changes were not captured by the model, including changes in fertility trends and changes in social contact patterns.<br>The model was calibrated to the demographic, behavioural, and epidemiological characteristics of the population of Norway. | |
| | **Perspective** | 1. Healthcare system<br>2. Societal | |
| | **Time horizon** | Base case 50yrs (up to 100yrs) | |
| | **Comparator** | No vaccination | |
| | **Discount rates** | 3% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | 1st dose: monovalent; 2nd dose: monovalent/quadrivalent MMRV | |
| | **Age at vaccination** | 1st dose at 15mths; 2nd dose at either 18mths/7yrs/11yrs (6 strategies in total) | |
| | **Coverage rate** | 95 to 97% for 2yr olds (base case value not clear) | |
| **Model input parameters** | **Efficacy/effectiveness** | Efficacy (GSK vaccines): 1-dose: 61.7%; 2-dose 94.6%<br>Efficacy (MSD vaccines): 1-dose: 90.3%; 2-dose 97% | |
| | **Waning** | Duration of immunity =25yrs after 1st dose and 77yrs after 2nd dose | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ Primary healthcare visits<br>▪ Hospitalisation<br>▪ Vaccine<br>▪ Administration of vaccine<br><br>**Indirect costs**<br>▪ Workdays lost due to varicella infection | **Measurement and valuation**<br>**Direct costs**<br>▪ Unit costs and rates of primary healthcare visits, hospitalisations as reported elsewhere<br>▪ List price of vaccine<br>▪ Nurse's time for administration (10 minutes per dose)<br><br>**Indirect costs**<br>▪ Mean wage for workdays lost |
| | **Effects included** | **Type of Effects**<br>**Direct effects**<br>▪ Incidence of varicella, BV and HZ<br>▪ Outpatient cases, hospitalisations and deaths<br><br>**Indirect effects**<br>▪ Incidence of HZ (exogenous boosting) | **Measurement and valuation**<br><br>**Indirect effects**<br>▪ Duration of boosting: 80yrs<br>▪ Assumed that persons who have low immunity to HZ are boosted when they come into contact with infectious persons at the same rate as susceptible persons become exposed with varicella<br><br>**Utilities and QALY loss per case**<br>▪ Varicella (by age: <15yrs; ≥15yrs)<br>▪ BV (by age: <15yrs; ≥15yrs)<br>▪ Mortality due to varicella (by age: <15yrs, 15-65yrs, ≥65yrs)<br>▪ Uncomplicated HZ (all ages)<br>▪ HZ with PHN (all ages) |
| **Economic results** | **Type of summary ratio** | ICER (Incremental cost/QALY gained) | |
| | **Overall payer perspective result** | Intervention dominant across all scenarios modelled | |
| | **Overall societal perspective result** | Intervention dominant across all scenarios modelled | |
| **Authors conclusions** | All modelled two-dose varicella vaccination strategies are projected to lead to substantial reductions in varicella disease and to be cost saving compared to no vaccination in Norway. | | |

**Key:** BV – breakthrough varicella; CUA – cost utility analysis; HZ – herpes zoster; MMRV – measles, mumps, rubella, varicella; NR – not reported; PHN – post herpetic neuralgia; QALY – quality adjusted life year;

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| **General study characteristics** | **Author Name, Year of Publication, DOI** | Rafferty et al. 2021[126] DOI: 10.1016/j.jval.2020.10.004 | |
| | **Region, Country** | Alberta, Canada | |
| | **Type of Economic Evaluation** | CUA | |
| | **Population** | Open population of 500,000 agents within a distance-based contact network comprising 'Rejectors' (3%), 'Hesitants' (30%) and 'Acceptors' (65%) | |
| | **Funding** | Alberta Health, Canada | |
| **Model characteristics** | **Model type** | Agent based model<br>Note: Contact patterns derived from POLYMOD data.[135] | |
| | **Perspective** | 1. Societal<br>2. Health care payer | |
| | **Time horizon** | 75yrs<br>Model run for 175yrs – the first 100yrs were to initialise the model to reach equilibrium without vaccination and the last 75yrs captured the costs and effects of 3 scenarios.<br>The ABM was previously fit to Alberta data before the implementation of chickenpox vaccination and checked for consistency with data post-vaccination | |
| | **Comparator** | No vaccination (versus both long- and short-dose intervals)<br>Short-dose interval (SDI) (versus long-dose interval [LDI]) | |
| | **Discount rates** | 1.5% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | NR | |
| | **Age at vaccination** | 1st dose at 12mths; 2nd dose at 18mths (SDI) or 4-6yrs (LDI) | |
| | **Coverage rate** | Based on agent's attitude to vaccines. (Rates below calibrated to chickenpox vaccination coverage rates in Alberta).<br>Probability of 1st dose vaccination: Rejectors (3%), Hesitants (75%), Acceptors (97%).<br>Probability of 2nd dose vaccination (conditional on 1st dose: Rejectors (33%), Hesitants (82%), Acceptors (98%). | |
| **Model input parameters** | **Efficacy/effectiveness** | Primary and secondary vaccine failure rates aligned with real-world effectiveness data. **Data not reported.** | |
| | **Waning** | NR | |
| | **Costs included** | **Type of cost**<br>**Direct medical costs**<br>▪ Physician visit (chickenpox and shingles)<br>▪ Hospital visit (chickenpox and shingles)<br>▪ Emergency room visit (chickenpox and shingles)<br>▪ Medication costs (chickenpox and shingles [including PHN])<br>▪ Personal expenses (chickenpox) [OTC and prescription medication, travel and gifts]<br><br>**Vaccination costs**<br>▪ Vaccine<br>▪ Febrile seizures (chickenpox)<br><br>**Indirect costs**<br>▪ Productivity loss for those ill with varicella and HZ (by age)<br>▪ Productivity loss for carers of those with varicella (by age) | **Measurement and valuation**<br>**Direct medical costs**<br>▪ % of chickenpox and shingles cases that will visit a physician and cost per case<br>▪ % of chickenpox and shingles cases that go to hospital (by age group), average length of stay and cost per day<br>▪ % of chickenpox and shingles cases that go to emergency room and cost per visit<br>▪ % of shingles cases who develop PHN (by age group) and % of cases that last for a certain number of days<br>▪ Average prescription cost per case of chickenpox and shingles<br>▪ Personal out of pocket expenses per case of chickenpox (by age group) and shingles<br><br>**Vaccination costs**<br>▪ Cost (procurement, labour and supply costs) to vaccinate a child with MMRV vaccine<br>▪ % of 1st dose chickenpox vaccinations that result in febrile seizure and cost to treat febrile seizure in emergency room<br><br>**Indirect costs**<br>▪ Cost per case of chickenpox<br>▪ Cost per case for hospitalisation with chickenpox<br>▪ Cost per case of shingles with no PHN<br>▪ Cost per case of shingles with PHN<br>▪ Cost per hospitalised case of shingles |

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| | **Effects included** | **Type of Effects**<br>**Direct effects**<br>▪ Incidence of varicella and BV<br>▪ Hospitalised cases of chickenpox<br>▪ Deaths<br><br>**Indirect effects**<br>▪ Main model run twice, once to include and once to exclude impact on incidence of HZ (exogenous boosting [EB]) | **Measurement and valuation**<br>**Boosting**<br>▪ Duration of boosting to HZ: 5yrs (based on empirical data)<br><br>**Utilities for QALYs**<br>▪ Baseline utility weight for no pain<br>▪ Chickenpox (normal) utility weight by age<br>▪ Chickenpox (breakthrough) utility weight by age<br>▪ Chickenpox (hospitalised) utility weight by age<br>▪ Shingles (normal) utility weight<br>▪ Shingles (PHN) utility weight<br>▪ Shingles (hospitalised) utility weight |
| **Economic results** | **Type of summary ratio** | ICUR (Incremental cost/QALY gained) | |
| | **Overall payer perspective result** | SDI and LDI both cost-effective versus no vaccination (ICUR <$10,000/QALY gained) when the impact on shingles [EB] not included.<br>SDI and LDI both not cost-effective versus no vaccination (ICUR>$125,000/QALY gained) when the impact on shingles [EB] included.<br>SDI cost-effective versus long-dose schedule (ICUR <$29,000/QALY gained) when the impact on shingles [EB] included.<br>SDI cost-effective versus long-dose schedule (ICUR <$24,000/ QALY gained) when the impact on shingles [EB] not included. | |
| | **Overall societal perspective result** | SDI and LDI both dominant versus no vaccination with and without inclusion of impact on shingles [EB].<br>SDI cost-effective versus LDI (ICUR <$6,000/QALY gained) when the impact on shingles [EB] included.<br>SDI cost-effective versus LDI (ICUR <$4,500/QALY gained) when the impact on shingles [EB] not included. | |
| **Authors conclusions** | Chickenpox vaccine was cost-effective when not considering shingles and remained so even if there was a minor increase in shingles following vaccination. However, if chickenpox vaccination did lead to a substantial increase in shingles, then chickenpox vaccination was not cost-effective from the healthcare perspective. | | |

**Key:** ABM – agent-based model; BV – breakthrough varicella; CUA – cost utility analysis; HZ – herpes zoster; ICUR – incremental cost utility ratio; MMRV – measles, mumps, rubella, varicella; LDI – long-dose interval; PHN – post herpetic neuralgia; QALY – quality adjusted life year; SDI – short-dose interval;

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| **General study characteristics** | **Author Name, Year of Publication, DOI** | van Lier et al. 2015[128] DOI: 10.1016/j.ebiom.2015.08.017 | |
| | **Region, Country** | the Netherlands | |
| | **Type of Economic Evaluation** | CEA | |
| | **Population** | Population of the Netherlands using demographic data from Statistics Netherlands (stationary population assumed from 2060 onwards) | |
| | **Funding** | National Institute for Public Health and the Environment (RIVM), the Netherlands | |
| **Model characteristics** | **Model type** | Age-structured transmission model<br>Note: Contact patterns sourced from POLYMOD study.[135] | |
| | **Perspective** | Societal | |
| | **Time horizon** | Up to 180yrs (ICERs calculated separately for each year to produce a timeline of cost-effectiveness) | |
| | **Comparator** | No vaccination | |
| | **Discount rates** | 4% for costs and 1.5% for outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | Monovalent | |
| | **Age at vaccination** | 1st dose at 12mths; 2nd dose at 4yrs | |
| | **Coverage rate** | 95% | |
| **Model input parameters** | **Efficacy/effectiveness** | Effectiveness: 1-dose 90%; 2-dose 95% | |
| | **Waning** | Not considered | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ GP visits (varicella and HZ)<br>▪ Hospitalisation (varicella and HZ)<br>▪ Medication<br>▪ Varicella vaccine cost<br>▪ Varicella vaccine introduction cost (e.g. new leaflets, campaign)<br>▪ Varicella vaccine coordination cost (e.g. variable personnel costs, other materials, printing)<br><br>**Indirect costs**<br>▪ Productivity loss due to acute illness by age (<15yrs [their parents] and 15-65yrs) (varicella and HZ)<br>▪ Productivity loss due to mortality by age (<15yrs and 15-65yrs) (varicella and HZ) | **Measurement and valuation**<br>**Direct costs**<br>▪ % varicella cases visiting the GP (by age - <15yrs and ≥15yrs), % by consultation type (at GP practice, telephone, home visit, central GP point), unit cost per consultation type<br>▪ % of HZ cases visiting the GP, unit cost per visit<br>▪ % of varicella GP visits requiring ED visit (by age - <15yrs and ≥15yrs) unit cost per visit<br>▪ % of varicella GP visits requiring medical specialist consultation (by age - <15yrs and ≥15yrs), unit cost per visit<br>▪ % of all varicella cases requiring hospitalisation (by age - <15yrs and ≥15yrs), % of all HZ cases requiring hospitalisation, unit cost per day for academic/general hospital, mean duration of stay<br>▪ % of all varicella and HZ cases requiring hospitalisation with ICU, unit cost per day for academic/general hospital, mean duration of stay<br>▪ % of all varicella cases requiring OTC medication for antipyretics, unit cost per case<br>▪ % of all varicella cases requiring OTC medication for skin, unit cost per case<br>▪ % of all GP visits for varicella requiring antibiotics, unit cost per treatment<br>▪ number of doses of immunoglobulin for varicella (for 0yr olds and women of reproductive age) required per year at baseline, unit cost per dose<br><br>**Vaccination costs**<br>▪ Once-off cost for vaccine introduction<br>▪ 2 doses of vaccine per vaccine, unit cost per dose<br>▪ Unit cost of vaccine coordination per vaccination<br><br>**Indirect costs**<br>▪ % of all cases with productivity loss for parents of <15yr olds with varicella, number of hours lost, mean unit cost per hour<br>▪ all cases for productivity loss due to acute illness for 15-65yr olds |

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| | | | (varicella and HZ), number of hours lost, unit cost per hour depending on age<br>▪ % of all cases with productivity loss due to mortality (varicella and HZ) by age (15-65yrs and ≥65yrs) |
| | **Effects included** | **Type of Effects**<br>**Direct effects**<br>▪ Incidence of varicella and HZ<br>▪ Deaths<br>▪ Vaccine induced VZV reactivation (included in 2/4 scenarios modelled)<br>▪ Outcomes aggregated to produce QALYs<br><br>**Indirect effects**<br>▪ Impact on incidence of HZ (exogenous boosting – included in 2/4 scenarios modelled) | **Measurement and valuation**<br>**QALY loss per case**<br>▪ Varicella (by age: 0-14yrs; ≥15yrs)<br>▪ BV (only <15yrs)<br>▪ Mortality due to varicella (by age: <15yrs, 15-65yrs, ≥65yrs)<br>▪ HZ acute illness (by age: 20yrs, 40yrs, 60yrs, 80yrs)<br>▪ Mortality due to HZ (by age: <15yrs, 15-65yrs, ≥65yrs) |
| **Economic results** | **Type of summary ratio** | ICER (Incremental cost/QALY gained) | |
| | **Overall societal perspective result** | ICERs unclear as only reported graphically.<br>Suggests that varicella vaccination is predominantly cost-effective (ICER <€20,000/QALY gained) and dominant versus no vaccination when exogenous boosting is not assumed and vaccine VZV reactivation is not assumed.<br>Suggests that varicella vaccination is predominantly cost-effective (ICER <€20,000/QALY gained) versus no vaccination when exogenous boosting is not assumed and vaccine VZV reactivation is assumed.<br>Suggests that varicella vaccination is predominantly dominated versus no vaccination when exogenous boosting is assumed and vaccine VZV reactivation is not assumed.<br>Suggests that varicella vaccination is dominated versus no vaccination when exogenous boosting is assumed and vaccine VZV reactivation is assumed. | |
| **Authors conclusions** | Cost-effectiveness of varicella vaccination depends strongly on the impact on HZ and the economic time horizon. Our findings reveal ethical dilemmas as varicella vaccination may result in unequal distribution of health effects between generations. | | |

**Key:** BV – breakthrough varicella; CEA – cost effectiveness analysis; HZ – herpes zoster; ICER – incremental cost effectiveness ratio; MMRV – measles, mumps, rubella, varicella; PHN – post herpetic neuralgia; QALY – quality adjusted life year; VZV – varicella zoster virus

| | | | |
|---|---|---|---|
| **General study characteristics** | **Author Name, Year of Publication, DOI** | Wolff et al. 2021[130] DOI: 10.1371/journal.pone.0251644 | |
| | **Country** | Sweden | |
| | **Type of Economic Evaluation** | CUA | |
| | **Population** | Hypothetical cohort of children aged 12mths | |
| | **Funding** | None | |
| **Model characteristics** | **Model type** | Age-structured dynamic Markov transmission model<br>Note: The contact patterns between age groups were based on a synthetic matrix derived from age specific contact patterns and validated through comparison with POLYMOD results.[135] | |
| | **Perspective** | 1. Societal<br>2. Health care payer | |
| | **Time horizon** | 85yrs | |
| | **Comparator** | No vaccination | |
| | **Discount rates** | 3% for costs and outcomes | |
| **Intervention strategy** | **Dosing schedule** | 2-dose | |
| | **Vaccine type** | NR | |
| | **Age at vaccination** | 1st dose at 12mths; 2nd dose at 18mths | |
| | **Coverage rate** | 95% | |
| **Model input parameters** | **Efficacy/effectiveness** | Effectiveness: 1-dose 81%; 2-dose 92% | |
| | **Waning** | 2% p.a. after the first dose; no waning after the 2nd dose | |
| | **Costs included** | **Type of cost**<br>**Direct costs**<br>▪ Vaccine<br>▪ Vaccine administration<br>▪ Primary care consultation for varicella and HZ (including PHN) (by age)<br>▪ Specialist care for varicella (by age)<br>▪ Hospitalisation for varicella and HZ (by age)<br>▪ Antivirals for HZ and medication for PHN<br>▪ Hospitalisation for stroke as a complication of HZ<br><br>**Indirect costs**<br>▪ Productivity loss for those ill with varicella and HZ (by age)<br>▪ Productivity loss for carers of those with varicella (by age) | **Measurement and valuation**<br>**Direct costs**<br>▪ List price of vaccine<br>▪ Nurse's time for administration (15 minutes per dose)<br>▪ Healthcare resource use obtained from study on burden of chickenpox and expert opinion and unit costs obtained from a regional hospital price list<br>▪ List price of antivirals and medication for HZ<br><br>**Indirect costs**<br>▪ Average monthly salary + statutory employer's fee |
| | **Effects included** | **Type of Effects**<br>**Direct effects**<br>▪ Incidence of varicella, BV and HZ<br>▪ Outpatient cases<br>▪ Hospitalisations<br><br>**Indirect effects**<br>▪ Incidence of HZ (exogenous boosting) (assumed comparable to live HZ vaccination of limited duration) | **Measurement and valuation**<br><br>**QALY loss per case**<br>▪ Varicella (by age)<br>▪ BV (by age)<br>▪ HZ (by age) |
| **Economic results** | **Type of summary ratio** | (ICER) Incremental cost/QALY gained | |
| | **Overall payer perspective result** | Intervention dominant | |
| | **Overall societal perspective result** | Intervention dominant | |
| **Authors conclusions** | The results from the health economic modelling suggest that it was cost-effective to introduce varicella vaccination in Sweden. | | |

**Key:** BV – breakthrough varicella; CUA – cost utility analysis; HZ – herpes zoster; NR – not reported; PHN – post herpetic neuralgia; QALY – quality adjusted life year;

# Appendix A7.1 Differential equations

### Age Group 1 (before vaccination)

$dS_1/dt = bN - \lambda_1 S_1 - \alpha_1 S_1 - \mu_1 S_1$ , $\quad where\ \lambda_1 = \sum_{j=1}^{16} pc_{1j}\left(I_j/N_j\right)$

$dE_1/dt = \lambda_1 S_1 - \sigma E_1 - \alpha_1 E_1 - \mu_1 E_1$

$dI_1/dt = \sigma E_1 - \gamma I_1 - \alpha_1 I_1 - \mu_1 I_1$

$dR_1/dt = \gamma I_1 - \delta R_1 + g_1\lambda_1 SZ_1 - \alpha_1 R_1 - \mu_1 R_1$

$dSZ_1/dt = \delta R_1 - \rho_1 SZ_1 - g_1\lambda_1 SZ_1 - \alpha_1 SZ_1 - \mu_1 SZ_1$

$dIZ_1/dt = \rho_1 SZ_1 - \gamma_z IZ_1 - \alpha_1 IZ_1 - \mu_1 IZ_1$

$dRZ_1/dt = \gamma_z IZ_1 - \alpha_1 RZ_1 - \mu_1 RZ_1$

$dD_1/dt = \mu_1 S_1 + \mu_1 E_1 + \mu_1 I_1 + \mu_1 R_1 + \mu_1 SZ_1 + \mu_1 IZ_1 + \mu_1 RZ_1$

### Age Group 2 (assumed first dose vaccination)

$dS_2/dt = \alpha_1 S_1 - cv1*(1-vf1)*ve1*a_1 S_1 - cv1*(1-vf1)*(1-ve1)*a_1 S_1 - cv1*vf1*a_1 S_1 - \lambda_2*(1-cv1)*a_1 S_1 - \lambda_2 S_2 - \alpha_2 S_2 - \mu_2 S_2$ , $\quad where\ \lambda_2 = \sum_{j=1}^{16} pc_{2j}\left(I_j/N_j\right)$

$dE_2/dt = \alpha_1 E_1 + \lambda_2*(1-cv1)*a_1 S_1 + \lambda_2 VFS_2 + \lambda_2 S_2 - \sigma E_2 - \alpha_2 E_2 - \mu_2 E_2$

$dI_2/dt = \alpha_1 I_1 + \sigma E_2 - \gamma I_2 - \alpha_2 I_2 - \mu_2 I_2$

$dR_2/dt = \alpha_1 R_1 + \gamma I_2 - \delta R_2 + g_2\lambda_2 SZ_2 - \alpha_2 R_2 - \mu_2 R_2$

$dSZ_2/dt = \alpha_1 SZ_1 + \delta R_2 - \rho_2 SZ_2 - g_2\lambda_2 SZ_2 - \alpha_2 SZ_2 - \mu_2 SZ_2$

$dIZ_2/dt = \alpha_1 IZ_1 + \rho_2 SZ_2 - \gamma_z IZ_2 - \alpha_2 IZ_2 - \mu_2 IZ_2$

$dRZ_2/dt = \alpha_1 RZ_1 + \gamma_z IZ_2 - \alpha_2 RZ_2 - \mu_2 RZ_2$

$dV1P_2/dt = cv1*(1-vf1)*ve1*a_1 S_1 - w1*V1P_2 - \alpha_2 V1P_2 - \mu_2 V1P_2$

$dVFS_2/dt = cv1*vf1*a_1 S_1 - \lambda_2 VFS_2 - \alpha_2 VFS_2 - \mu_2 VFS_2$

$dVS_2/dt = cv1*(1-vf1)*(1-ve1)*a_1 S_1 + w1*V1P_2 - v\lambda_2 VS_2 - \alpha_2 VS_2 - \mu_2 VS_2$

$dVE_2/dt = v\lambda_2 VS_2 - \sigma VE_2 - \alpha_2 VE_2 - \mu_2 VE_2$

$dVI_2/dt = \sigma VE_2 - \gamma VI_2 - \alpha_2 VI_2 - \mu_2 VI_2$

$dVR_2/dt = \gamma VI_2 - \delta VR_2 + g_2\lambda_2 VSZ_2 - \alpha_2 VR_2 - \mu_2 VR_2$

$dVSZ_2/dt = \delta VR_2 - v\rho_2 VSZ_2 - g_2\lambda_2 VSZ_2 - \alpha_2 VSZ_2 - \mu_2 VSZ_2$

$dVIZ_2/dt = v\rho_2 VSZ_2 - \gamma_z VIZ_2 - \alpha_2 VIZ_2 - \mu_2 VIZ_2$

$dVRZ_2/dt = \gamma_z VIZ_2 - \alpha_2 VRZ_2 - \mu_2 VRZ_2$

$dD_2/dt = \mu_2 S_2 + \mu_2 E_2 + \mu_2 I_2 + \mu_2 R_2 + \mu_2 V1P_2 + \mu_2 VFS_2 + \mu_2 VS_2 + \mu_2 VE_2 + \mu_2 VI_2 + \mu_2 VR_2 + \mu_2 SZ_2 + \mu_2 IZ_2 + \mu_2 RZ_2$

$$dVD_2/dt = \mu_2 V1P_2 + \mu_2 VFS_2 + \mu_2 VS_2 + \mu_2 VE_2 + \mu_2 VI_2 + \mu_2 VR_2 + \mu_2 VSZ_2 + \mu_2 VIZ_2 + \mu_2 VRZ_2$$

**Age Group 3 (assumed second dose vaccination)**

$$dS_3/dt = \alpha_2 S_2 - \lambda_3 S_3 - \alpha_3 S_3 - \mu_3 S_3 , \qquad where\ \lambda_3 = \sum_{j=1}^{16} pc_{3j}\left(I_j/N_j\right)$$

$$dE_3/dt = \alpha_2 E_2 + \lambda_3 S_3 + \lambda_3 VFS_3 - \sigma E_3 - \alpha_3 E_3 - \mu_3 E_3$$

$$dI_3/dt = \alpha_2 I_2 + \sigma E_3 - \gamma I_3 - \alpha_3 I_3 - \mu_3 I_3$$

$$dR_3/dt = \alpha_2 R_2 + \gamma I_3 - \delta R_3 + g_3\lambda_3 SZ_3 - \alpha_3 R_3 - \mu_3 R_3$$

$$dSZ_3/dt = \alpha_2 SZ_2 + \delta R_3 - \rho_3 SZ_3 - g_3\lambda_3 SZ_3 - \alpha_3 SZ_3 - \mu_3 SZ_3$$

$$dIZ_3/dt = \alpha_2 IZ_2 + \rho_3 SZ_3 - \gamma_z IZ_3 - \alpha_3 IZ_3 - \mu_3 IZ_3$$

$$dRZ_3/dt = \alpha_2 RZ_2 + \gamma_z IZ_3 - \alpha_3 RZ_3 - \mu_3 RZ_3$$

$$dV1P_3/dt = a_2 V1P_2 - cv2 * (1 - vf2) * a_2 VIP_2 - w1 * V1P_3 - \alpha_3 V1P_3 - \mu_3 V1P_3$$

$$dV1Q_3/dt = cv2 * (1 - vf2) * ve1 * a_2 VFS_2 - w1 * V1Q_3 - \alpha_3 V1Q_3 - \mu_3 V1Q_3$$

$$dV2P_3/dt = cv2 * (1 - vf2) * a_2 VIP_2 + cv2 * (1 - vf2) * ve2 * a_2 VS_2 - \alpha_3 V2P_3 - \mu_2 V2P_3$$

$$dVFS_3/dt = a_2 VFS_2 - cv2 * (1 - vf2) * ve1 * a_2 VFS_2 - cv2 * (1 - vf2) * (1 - ve1) * a_2 VFS_2 - \lambda_3 VFS_3 - \alpha_3 VFS_3 - \mu_3 VFS_3$$

$$dVS_3/dt = a_2 VS_2 - cv2 * (1 - vf2) * ve2 * a_2 VS_2 + cv2 * (1 - vf2) * (1 - ve1) * a_2 VFS_2 + w1 * V1P_3 + w1 * V1Q_3 - v\lambda_3 VS_3 - \alpha_3 VS_3 - \mu_3 VS_3$$

$$dVE_3/dt = \alpha_2 VE_2 + v\lambda_3 VS_3 - \sigma VE_3 - \alpha_3 VE_3 - \mu_3 VE_3$$

$$dVI_3/dt = \alpha_2 VI_2 + \sigma VE_3 - \gamma VI_3 - \alpha_3 VI_3 - \mu_3 VI_3$$

$$dVR_3/dt = \alpha_2 VR_2 + \gamma VI_3 - \delta VR_3 + g_3\lambda_3 VSZ_3 - \alpha_3 VR_3 - \mu_3 VR_3$$

$$dVSZ_3/dt = \alpha_2 VSZ_2 + \delta VR_3 - v\rho_3 VSZ_3 - g_3\lambda_3 VSZ_3 - \alpha_3 VSZ_3 - \mu_3 VSZ_3$$

$$dVIZ_3/dt = \alpha_2 VIZ_2 + v\rho_3 VSZ_3 - \gamma_z VIZ_3 - \alpha_3 VIZ_3 - \mu_3 VIZ_3$$

$$dVRZ_3/dt = \alpha_2 VRZ_2 + \gamma_z VIZ_3 - \alpha_3 VRZ_3 - \mu_3 VRZ_3$$

$$dD_3/dt = \mu_3 S_3 + \mu_3 E_3 + \mu_3 I_3 + \mu_3 R_3 + \mu_3 SZ_3 + \mu_3 IZ + \mu_3 RZ_3$$

$$dVD_3/dt = \mu_3 V1P_3 + \mu_3 V1Q_3 + \mu_3 V2P_3 + \mu_3 VFS_3 + \mu_3 VS_3 + \mu_3 VE_3 + \mu_3 VI_3 + \mu_3 VR_3 + \mu_3 VSZ_3 + \mu_3 VIZ + \mu_3 VRZ_3$$

**Age Groups after vaccination (excluding final age group)**

$$dS_i/dt = \alpha_{i-1} S_{i-1} - \lambda_i S_i - \alpha_i S_i - \mu_i S_i , \qquad where\ \lambda_i = \sum_{j=1}^{16} pc_{ij}\left(I_j/N_j\right)$$

$$dE_i/dt = \alpha_{i-1} E_{i-1} + \lambda_i S_i + \lambda_i VFS_i - \sigma_i E_i - \alpha_i E_i - \mu_i E_i$$

$$dI_i/dt = \alpha_{i-1} I_{i-1} + \sigma_i E_i - \gamma_i I_i - \alpha_i I_i - \mu_i I_i$$

$$dR_i/dt = \alpha_{i-1} R_{i-1} + \gamma_i I_i - \delta R_i + g_i\lambda_i SZ_i - \alpha_i R_i - \mu_i R_i$$

$$dSZ_i/dt = \alpha_{i-1} SZ_{i-1} + \delta R_i - \rho_i SZ_i - g_i\lambda_i SZ_i - \alpha_i SZ_i - \mu_i SZ_i$$

$$dIZ_i/dt = \alpha_{i-1}IZ_{i-1} + \rho_i SZ_i - \gamma_z IZ_i - \alpha_i IZ_i - \mu_i IZ_i$$
$$dRZ_i/dt = \alpha_{i-1}RZ_{i-1} + \gamma_z IZ_i - \alpha_i RZ_i - \mu_i RZ_i$$
$$dV1P_i/dt = a_{i-1}V1P_{i-1} - w1 * V1P_i - \alpha_i V1P_i - \mu_i V1P_i$$
$$dV1Q_i/dt = a_{i-1}V1Q_{i-1} - w1 * V1Q_i - \alpha_i V1Q_i - \mu_i V1Q_i$$
$$dV2P_i/dt = a_{i-1}V2P_{i-1} - \alpha_i V2P_i - \mu_i V2P_i$$
$$dVFS_i/dt = a_{i-1}VFS_{i-1} - \lambda_i VFS_i - \alpha_i VFS_i - \mu_i VFS_i$$
$$dVS_i/dt = a_{i-1}VS_{i-1} + w1 * V1P_i + w1 * V1Q_i + w1 * V2P_i - v\lambda_i VS_i - \alpha_i VS_i - \mu_i VS_i$$
$$dVE_i/dt = \alpha_{i-1}VE_{i-1} + v\lambda_i VS_i - \sigma VE_i - \alpha_i VE_i - \mu_i VE_i$$
$$dVI_i/dt = \alpha_{i-1}VI_{i-1} + \sigma VE_i - \gamma VI_i - \alpha_i VI_i - \gamma VI_i$$
$$dVR_i/dt = \alpha_{i-1}VR_{i-1} + \gamma VI_i - \delta VR_i + g_i\lambda_i VSZ_i - \alpha_i VR_i - \mu_i VR_i$$
$$dVSZ_i/dt = \alpha_{i-1}VSZ_{i-1} + \delta VR_i - v\rho_i VSZ_i - g_i\lambda_i VSZ_i - \alpha_i VSZ_i - \mu_i VSZ_i$$
$$dVIZ_i/dt = \alpha_{i-1}VIZ_{i-1} + v\rho_i VSZ_i - \gamma_z VIZ_i - \alpha_i VIZ_i - \mu_i VIZ_i$$
$$dVRZ_i/dt = \alpha_{i-1}VRZ_{i-1} + \gamma_z VIZ_i - \alpha_i VRZ_i - \mu_i VRZ_i$$
$$dD_i/dt = \mu_i S_i + \mu_i E_i + \mu_i I_i + \mu_i R_i + \mu_i SZ_i + \mu_i IZ_i + \mu_i RZ_i$$
$$dD_i/dt = \mu_i V1P_i + \mu_i V1Q_i + \mu_i V2P_i + \mu_i VFS_i + \mu_i VS_i + \mu_i VE_i + \mu_i VI_i + \mu_i VR_i + \mu_i VSZ_i + \mu_i VIZ_i + \mu_i VRZ_i$$

**Final age group (no ageing)**

$$dS_i/dt = \alpha_{i-1}S_{i-1} - \lambda_i S_i - \mu_i S_i \ ,$$
$$dE_i/dt = \alpha_{i-1}E_{i-1} + \lambda_i S_i + \lambda_i VFS_i - \sigma E_i - \mu_i E_i$$
$$dI_i/dt = \alpha_{i-1}I_{i-1} + \sigma E_i - \gamma I_i - \mu_i I_i$$
$$dR_i/dt = \alpha_{i-1}R_{i-1} + \gamma I_i - \delta R_i + g_i\lambda_i SZ_i - \mu_i R_i$$
$$dSZ_i/dt = \alpha_{i-1}SZ_{i-1} + \delta R_i - \rho_i SZ_i - g_i\lambda_i SZ_i - \mu_i SZ_i$$
$$dIZ_i/dt = \alpha_{i-1}IZ_{i-1} + \rho_i SZ_i - \gamma_z IZ_i - \mu_i IZ_i$$
$$dRZ_i/dt = \alpha_{i-1}RZ_{i-1} + \gamma_z IZ_i - \mu_i RZ_i$$
$$dV1P_i/dt = a_{i-1}V1P_{i-1} - w1 * V1P_i - \mu_i V1P_i$$
$$dV1Q_i/dt = a_{i-1}V1Q_{i-1} - w1 * V1Q_i - \mu_i V1Q_i$$
$$dV2P_i/dt = a_{i-1}V2P_{i-1} - \mu_i V2P_i$$
$$dVFS_i/dt = a_{i-1}VFS_{i-1} - \lambda_i VFS_i - \mu_x VFS_x$$
$$dVS_i/dt = a_{i-1}VS_{i-1} + w1 * V1P_i + w1 * V1Q_i - v\lambda_i VS_i - \mu_i VS_i$$

$$dVE_i/dt = \alpha_{i-1}VE_{i-1} + v\lambda_i VS_i - \sigma VE_i - \mu_i VE_i$$

$$dVI_i/dt = \alpha_{i-1}VI_{i-1} + \sigma VE_x - \gamma VI_i - \mu_i VI_i$$

$$dVR_i/dt = \alpha_{i-1}VR_{i-1} + \gamma VI_i - \delta VR_i + g_i\lambda_i VSZ_i - \mu_i VR_i$$

$$dVSZ_i/dt = \alpha_{i-1}VSZ_{i-1} + \delta VR_i - v\rho_i VSZ_i - g_i\lambda_i VSZ_i - \mu_i VSZ_i$$

$$dVIZ_i/dt = \alpha_{i-1}VIZ_{i-1} + v\rho_i VSZ_i - \gamma_z VIZ_i - \mu_i VIZ_i$$

$$dVRZ_i/dt = \alpha_{i-1}VRZ_{i-1} + \gamma_z VIZ_i - \mu_i VRZ_i$$

$$dD_i/dt = \mu_i S_i + \mu_i E_i + \mu_i I_i + \mu_i R_i + \mu_i V1P_i + \mu_i ZS_i + \mu_i IZ_i + \mu_i RZ_i$$

$$dD_i/dt = \mu_i V1P_i + \mu_i V1Q_i + \mu_i V2P_i + \mu_i VFS_i + \mu_i VS_i + \mu_i VE_i + \mu_i VI_i + \mu_i VR_i + \mu_i VSZ_i + \mu_i VIZ_i + \mu_i VRZ_i$$

## Appendix A7.2 Contact matrix

| Age_groups | 0-<1yr | 12-14mths | 15-23mths | 2-<3yrs | 3-<4yrs | 4-<5yrs | 5-9yrs | 10-14yrs | 15-19yrs | 20-29yrs | 30-39yrs | 40-49yrs | 50-59yrs | 60-69yrs | 70-79yrs | ≥80yrs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0-<1yr | 0.400000 | 0.050000 | 0.150000 | 0.133333 | 0.333333 | 0.133333 | 0.600000 | 0.600000 | 0.266667 | 1.400000 | 2.266667 | 0.733333 | 0.800000 | 0.466667 | 0.066667 | 0.000000 |
| 12-14mths | 0.062500 | 0.125000 | 0.375000 | 0.062500 | 0.140625 | 0.015625 | 0.187500 | 0.109375 | 0.031250 | 0.515625 | 0.546875 | 0.250000 | 0.109375 | 0.078125 | 0.046875 | 0.000000 |
| 15-23mths | 0.187500 | 0.375000 | 0.125000 | 0.187500 | 0.421875 | 0.046875 | 0.562500 | 0.328125 | 0.093750 | 1.546875 | 1.640625 | 0.750000 | 0.328125 | 0.234375 | 0.140625 | 0.000000 |
| 2-<3yrs | 0.058824 | 0.088235 | 0.264706 | 0.117647 | 0.823529 | 0.235294 | 0.470588 | 0.235294 | 0.647059 | 1.411765 | 1.941177 | 1.588235 | 0.647059 | 0.176471 | 0.294118 | 0.000000 |
| 3-<4yrs | 0.071429 | 0.071429 | 0.214286 | 0.321429 | 1.071429 | 0.464286 | 0.750000 | 0.428571 | 0.392857 | 0.821429 | 1.785714 | 0.785714 | 0.642857 | 0.321429 | 0.178571 | 0.000000 |
| 4-<5yrs | 0.105263 | 0.026316 | 0.078947 | 0.105263 | 1.315789 | 0.947368 | 1.421053 | 0.894737 | 0.263158 | 0.578947 | 2.105263 | 0.684211 | 0.526316 | 0.578947 | 0.105263 | 0.000000 |
| 5-9yrs | 0.012658 | 0.025316 | 0.075949 | 0.177215 | 0.189873 | 0.227848 | 5.303798 | 1.240506 | 0.316456 | 0.949367 | 1.987342 | 1.594937 | 0.645570 | 0.367089 | 0.113924 | 0.050633 |
| 10-14yrs | 0.037383 | 0.018692 | 0.056075 | 0.074766 | 0.084112 | 0.121495 | 1.373832 | 7.261682 | 1.121495 | 0.728972 | 1.710280 | 1.831776 | 0.616822 | 0.317757 | 0.140187 | 0.056075 |
| 15-19yrs | 0.009615 | 0.016827 | 0.050481 | 0.048077 | 0.057692 | 0.105769 | 0.509615 | 1.432692 | 7.384615 | 1.865385 | 1.509615 | 1.769231 | 0.788462 | 0.413462 | 0.105769 | 0.019231 |
| 20-29yrs | 0.048387 | 0.028226 | 0.084677 | 0.137097 | 0.104839 | 0.177419 | 0.483871 | 0.387097 | 1.185484 | 3.701613 | 1.822581 | 1.693548 | 1.088710 | 0.500000 | 0.177419 | 0.048387 |
| 30-39yrs | 0.072000 | 0.028000 | 0.084000 | 0.112000 | 0.280000 | 0.160000 | 1.112000 | 0.648000 | 0.528000 | 1.680000 | 2.808000 | 1.936000 | 1.224000 | 0.640000 | 0.240000 | 0.048000 |
| 40-49yrs | 0.008197 | 0.014344 | 0.043033 | 0.090164 | 0.081967 | 0.040984 | 0.483607 | 0.836066 | 1.024590 | 1.672131 | 2.180328 | 2.786885 | 1.368853 | 0.672131 | 0.286885 | 0.172131 |
| 50-59yrs | 0.035088 | 0.015351 | 0.046053 | 0.052632 | 0.078947 | 0.061404 | 0.201754 | 0.254386 | 0.543860 | 1.763158 | 1.640351 | 1.736842 | 1.798246 | 0.894737 | 0.403509 | 0.350877 |
| 60-69yrs | 0.018182 | 0.004545 | 0.013636 | 0.072727 | 0.072727 | 0.036364 | 0.354546 | 0.372727 | 0.254546 | 1.118182 | 1.600000 | 1.454546 | 1.436364 | 1.172727 | 0.363636 | 0.236364 |
| 70-79yrs | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.068966 | 0.034483 | 0.172414 | 0.310345 | 0.620690 | 0.965517 | 0.655172 | 1.517241 | 0.931035 | 1.379310 | 1.103448 | 0.206897 |
| ≥80yrs | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.500000 | 0.000000 | 0.500000 | 0.000000 | 1.000000 | 0.000000 | 0.000000 | 1.000000 |

## Appendix A7.3 Economic model input parameters

| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| *Probability of primary care utilisation for varicella* | | | | |
| Probability GP visit for all varicella_age groups 1-6 | 8.0% | 5.0% | 9.0% | Health Protection Surveillance Centre[44] |
| Probability GP visit for all varicella_age groups 7-8 | 7.0% | 5.0% | 8.0% | |
| Probability GP visit for all varicella_age groups 9-14 | 25.0% | 21.0% | 32.0% | |
| Probability GP visit for all varicella_age groups 15-16 | 5.0% | 3.0% | 10.0% | |
| Probability GP visit for all varicella_age group 16 | 100% | 3.0% | 10.0% | |
| Probability GP visit for severe varicella | 100% | 100% | 100% | Assumed |
| *Probability of primary care utilisation for herpes zoster* | | | | |
| Probability GP visit for acute herpes zoster | 100% | 100% | 100% | Assumed |
| Probability GP visit for post herpetic neuralgia (PHN) | 100% | 100% | 100% | Assumed |
| Probability GP visit for severe herpes zoster | 100% | 100% | 100% | Assumed |
| *Probability public patient* | | | | |
| Probability GP visit public_age group 1 | 100% | 100% | 100% | Health Service Executive – Primary Care Reimbursement Service[170] |
| Probability GP visit public_age group 2 | 100% | 100% | 100% | |
| Probability GP visit public_age group 3 | 100% | 100% | 100% | Health Service Executive[168, 169] |
| Probability GP visit public_age group 4 | 100% | 100% | 100% | |
| Probability GP visit public_age group 5 | 100% | 100% | 100% | |
| Probability GP visit public_age group 6 | 100% | 100% | 100% | |
| Probability GP visit public_age group 7 | 46.1% | 46.1% | 46.1% | |
| Probability GP visit public_age group 8 | 43.8% | 43.8% | 43.8% | |
| Probability GP visit public_age group 9 | 24.8% | 24.8% | 24.8% | |
| Probability GP visit public_age group 10 | 22.8% | 22.8% | 22.8% | |
| Probability GP visit public_age group 11 | 22.8% | 22.8% | 22.8% | |
| Probability GP visit public_age group 12 | 27.4% | 27.4% | 27.4% | |
| Probability GP visit public_age group 13 | 32.5% | 32.5% | 32.5% | |
| Probability GP visit public_age group 14 | 39.2% | 39.2% | 39.2% | |
| Probability GP visit public_age group 15 | 100% | 100% | 100% | |
| Probability GP visit public_age group 16 | 100% | 100% | 100% | |
| Probability prescription medicines public_age group 1 | 20.8% | 20.8% | 20.8% | Health Service Executive – Primary Care Reimbursement Service[170] |
| Probability prescription medicines public_age group 2 | 20.8% | 20.8% | 20.8% | |
| Probability prescription medicines public_age group 3 | 20.8% | 20.8% | 20.8% | |
| Probability prescription medicines public_age group 4 | 20.8% | 20.8% | 20.8% | |
| Probability prescription medicines public_age group 5 | 20.8% | 20.8% | 20.8% | |
| Probability prescription medicines public_age group 6 | 20.8% | 20.8% | 20.8% | |
| Probability prescription medicines public_age group 7 | 31.9% | 31.9% | 31.9% | |
| Probability prescription medicines public_age group 8 | 34.4% | 34.4% | 34.4% | |
| Probability prescription medicines public_age group 9 | 21.3% | 21.3% | 21.3% | |
| Probability prescription medicines public_age group 10 | 20.3% | 20.3% | 20.3% | |
| Probability prescription medicines public_age group 11 | 20.5% | 20.5% | 20.5% | |
| Probability prescription medicines public_age group 12 | 24.5% | 24.5% | 24.5% | |
| Probability prescription medicines public_age group 13 | 29.8% | 29.8% | 29.8% | |
| Probability prescription medicines public_age group 14 | 36.6% | 36.6% | 36.6% | |
| Probability prescription medicines public_age group 15 | 72.4% | 72.4% | 72.4% | |
| Probability prescription medicines public_age group 16 | 82.7% | 82.7% | 82.7% | |
| *Probability over-the-counter (OTC) medication recommended for varicella* | | | | |

| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| Probability OTC medication recommended for non-severe varicella | 50% | 10% | 100% | Assumed |
| Probability OTC medication recommended for severe varicella | 100% | 50% | 100% | |
| Probability OTC medication recommended for breakthrough varicella | 50% | 10% | 100% | |
| *Probability prescription medication prescribed by GP for herpes zoster and PHN* | | | | |
| Probability medication prescribed by GP for acute herpes zoster_age groups 1-9 | 50% | 10% | 50% | Assumed |
| Probability medication prescribed by GP for PHN_age groups 1-9 | 50% | 10% | 50% | |
| Probability medication prescribed by GP for severe herpes zoster_age groups 1-9 | 50% | 10% | 50% | |
| Probability medication prescribed by GP for acute herpes zoster_age groups 10-16 | 100% | 50% | 100% | Assumed all adults presenting to GP with herpes zoster and PHN are prescribed medication. |
| Probability medication prescribed by GP for PHN_age groups 10-16 | 100% | 50% | 100% | |
| Probability medication prescribed by GP for severe herpes zoster_age groups 10-16 | 100% | 50% | 100% | |
| *Disease severity probability - varicella* | | | | |
| Probability severe (hospitalised) varicella_age group 1 | 1.17% | 0.82% | 1.75% | Hospital Inpatient Enquiry (HIPE) System Discharge Data[163] |
| Probability severe (hospitalised) varicella_age group 2 | 0.22% | 0.13% | 0.35% | |
| Probability severe (hospitalised) varicella_age group 3 | 0.22% | 0.13% | 0.35% | |
| Probability severe (hospitalised) varicella_age group 4 | 0.42% | 0.18% | 0.69% | |
| Probability severe (hospitalised) varicella_age group 5 | 0.41% | 0.19% | 0.61% | |
| Probability severe (hospitalised) varicella_age group 6 | 0.41% | 0.12% | 0.76% | |
| Probability severe (hospitalised) varicella_age group 7 | 0.51% | 0.30% | 0.68% | |
| Probability severe (hospitalised) varicella_age group 8 | 0.26% | 0.12% | 0.68% | |
| Probability severe (hospitalised) varicella_age group 9 | 0.26% | 0.12% | 0.40% | |
| Probability severe (hospitalised) varicella_age group 10 | 0.79% | 0.27% | 1.44% | |
| Probability severe (hospitalised) varicella_age group 11 | 0.79% | 0.27% | 1.44% | |
| Probability severe (hospitalised) varicella_age group 12 | 2.80% | 2.42% | 4.30% | |
| Probability severe (hospitalised) varicella_age group 13 | 2.80% | 2.42% | 4.30% | |
| Probability severe (hospitalised) varicella_age group 14 | 12.7% | 6.67% | 20.00% | |
| Probability severe (hospitalised) varicella_age group 15 | 12.7% | 6.67% | 20.00% | |
| Probability severe (hospitalised) varicella_age group 16 | 100% | 65.86% | 100% | |
| *Disease severity probability - herpes zoster* | | | | |
| Probability PHN in cases of acute herpes zoster_age group 1 | 3.23% | 2.84% | 3.64% | Thompson et al.[160] |
| Probability PHN in cases of acute herpes zoster_age group 2 | 3.23% | 2.84% | 3.64% | |
| Probability PHN in cases of acute herpes zoster_age group 3 | 3.23% | 2.84% | 3.64% | |
| Probability PHN in cases of acute herpes zoster_age group 4 | 3.23% | 2.84% | 3.64% | |
| Probability PHN in cases of acute herpes zoster_age group 5 | 3.23% | 2.84% | 3.64% | |
| Probability PHN in cases of acute herpes zoster_age group 6 | 3.23% | 2.84% | 3.64% | |
| Probability PHN in cases of acute herpes zoster_age group 7 | 3.23% | 2.84% | 3.64% | |
| Probability PHN in cases of acute herpes zoster_age group 8 | 3.24% | 3.02% | 3.49% | |
| Probability PHN in cases of acute herpes zoster_age group 9 | 3.24% | 3.02% | 3.49% | |
| Probability PHN in cases of acute herpes zoster_age group 10 | 5.04% | 4.80% | 5.27% | |
| Probability PHN in cases of acute herpes zoster_age group 11 | 7.06% | 6.86% | 7.26% | |
| Probability PHN in cases of acute herpes zoster_age group 12 | 8.73% | 8.55% | 8.91% | |
| Probability PHN in cases of acute herpes zoster_age group 13 | 10.90% | 10.73% | 11.06% | |
| Probability PHN in cases of acute herpes zoster_age group 14 | 15.50% | 15.30% | 15.72% | |
| Probability PHN in cases of acute herpes zoster_age group 15 | 22.65% | 22.43% | 22.87% | |
| Probability PHN in cases of acute herpes zoster_age group 16 | 22.65% | 22.43% | 22.87% | |
| Probability severe (hospitalised) herpes zoster_age group 1 | 6.02% | 4.07% | 8.72% | Hospital Inpatient Enquiry (HIPE) System Discharge Data[163] |
| Probability severe (hospitalised) herpes zoster_age group 2 | 6.02% | 4.07% | 8.72% | |
| Probability severe (hospitalised) herpes zoster_age group 3 | 6.02% | 4.07% | 8.72% | |
| Probability severe (hospitalised) herpes zoster_age group 4 | 6.02% | 4.07% | 8.72% | |

| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| Probability severe (hospitalised) herpes zoster_age group 5 | 6.02% | 4.07% | 8.72% | |
| Probability severe (hospitalised) herpes zoster_age group 6 | 6.02% | 4.07% | 8.72% | |
| Probability severe (hospitalised) herpes zoster_age group 7 | 6.02% | 4.07% | 8.72% | |
| Probability severe (hospitalised) herpes zoster_age group 8 | 2.96% | 1.23% | 4.74% | |
| Probability severe (hospitalised) herpes zoster_age group 9 | 2.96% | 1.23% | 4.74% | |
| Probability severe (hospitalised) herpes zoster_age group 10 | 1.45% | 0.22% | 2.82% | |
| Probability severe (hospitalised) herpes zoster_age group 11 | 2.09% | 1.32% | 3.63% | |
| Probability severe (hospitalised) herpes zoster_age group 12 | 1.64% | 1.01% | 2.18% | |
| Probability severe (hospitalised) herpes zoster_age group 13 | 1.21% | 0.74% | 1.93% | |
| Probability severe (hospitalised) herpes zoster_age group 14 | 1.56% | 0.98% | 2.25% | |
| Probability severe (hospitalised) herpes zoster_age group 15 | 1.45% | 0.83% | 2.07% | |
| Probability severe (hospitalised) herpes zoster_age group 16 | 0.84% | 0.45% | 1.06% | |
| *Direct medical costs - varicella* | | | | |
| Cost of GP visit for varicella_public | €49.72 | €39.78 | €59.66 | Smith et al.[171] |
| Cost of GP visit for varicella_private | €54.05 | €43.24 | €64.86 | Lower and upper bounds +/-20%. |
| Cost of OTC medication for varicella_age groups 1-3 | €13.90 | €11.12 | €16.68 | Calculated. |
| Cost of OTC medication for varicella_age groups 4-8 | €17.90 | €14.32 | €21.48 | Lower and upper bounds +/-20%. |
| Cost of OTC medication for varicella_age groups 9-16 | €11.20 | €8.96 | €13.44 | |
| Cost of hospitalisation for severe varicella_age group 1 | €3,524 | €2,819 | €4,229 | Hospital Inpatient Enquiry (HIPE) System Discharge Data[163] and Activity Based Funding Admitted Patient Price List.[173] Lower and upper bounds +/-20%. |
| Cost of hospitalisation for severe varicella_age group 2 | €3,827 | €3,062 | €4,592 | |
| Cost of hospitalisation for severe varicella_age group 3 | €3,827 | €3,062 | €4,592 | |
| Cost of hospitalisation for severe varicella_age group 4 | €4,136 | €3,309 | €4,963 | |
| Cost of hospitalisation for severe varicella_age group 5 | €4,239 | €3,391 | €5,087 | |
| Cost of hospitalisation for severe varicella_age group 6 | €4,192 | €3,354 | €5,030 | |
| Cost of hospitalisation for severe varicella_age group 7 | €4,057 | €3,246 | €4,868 | |
| Cost of hospitalisation for severe varicella_age group 8 | €3,797 | €3,038 | €4,556 | |
| Cost of hospitalisation for severe varicella_age group 9 | €3,797 | €3,038 | €4,556 | |
| Cost of hospitalisation for severe varicella_age group 10 | €4,451 | €3,561 | €5,341 | |
| Cost of hospitalisation for severe varicella_age group 11 | €4,451 | €3,561 | €5,341 | |
| Cost of hospitalisation for severe varicella_age group 12 | €5,484 | €4,387 | €6,581 | |
| Cost of hospitalisation for severe varicella_age group 13 | €5,484 | €4,387 | €6,581 | |
| Cost of hospitalisation for severe varicella_age group 14 | €7,714 | €6,171 | €9,257 | |
| Cost of hospitalisation for severe varicella_age group 15 | €7,714 | €6,171 | €9,257 | |
| Cost of hospitalisation for severe varicella_age group 16 | €7,455 | €5,964 | €8,946 | |
| *Direct medical costs - herpes zoster* | | | | |
| Cost of GP for herpes zoster | €88.18 | €70.54 | €105.82 | Crosbie et al.[161] |
| Cost of GP for PHN | €94.23 | €75.38 | €113.08 | Lower and upper bounds +/-20%. |
| Cost of GP for severe herpes zoster | €88.18 | €70.54 | €105.82 | Assumed the same cost as for acute herpes zoster. Lower and upper bounds +/-20%. |
| Cost of prescription medication for acute herpes zoster | €104.62 | €83.70 | €125.54 | Crosbie et al.[161] |
| Cost of prescription medication for PHN | €101.88 | €81.50 | €122.26 | Lower and upper bounds +/-20%. |
| Cost of prescription medication for severe herpes zoster | €104.62 | €83.70 | €125.54 | Assumed the same cost as for acute herpes zoster. Lower and upper bounds +/-20%. |
| Cost of hospitalisation for severe herpes zoster_age group 1 | €4,598 | €3,678 | €5,518 | Hospital Inpatient Enquiry (HIPE) System Discharge Data[163] and Activity Based Funding Admitted Patient Price List.[173] Lower and upper bounds +/-20%. |
| Cost of hospitalisation for severe herpes zoster_age group 2 | €4,598 | €3,678 | €5,518 | |
| Cost of hospitalisation for severe herpes zoster_age group 3 | €4,598 | €3,678 | €5,518 | |
| Cost of hospitalisation for severe herpes zoster_age group 4 | €4,598 | €3,678 | €5,518 | |
| Cost of hospitalisation for severe herpes zoster_age group 5 | €4,598 | €3,678 | €5,518 | |

| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| Cost of hospitalisation for severe herpes zoster_age group 6 | €4,598 | €3,678 | €5,518 | |
| Cost of hospitalisation for severe herpes zoster_age group 7 | €4,598 | €3,678 | €5,518 | |
| Cost of hospitalisation for severe herpes zoster_age group 8 | €5,207 | €4,166 | €6,248 | |
| Cost of hospitalisation for severe herpes zoster_age group 9 | €5,207 | €4,166 | €6,248 | |
| Cost of hospitalisation for severe herpes zoster_age group 10 | €5,280 | €4,224 | €6,336 | |
| Cost of hospitalisation for severe herpes zoster_age group 11 | €5,826 | €4,661 | €6,991 | |
| Cost of hospitalisation for severe herpes zoster_age group 12 | €5,574 | €4,459 | €6,688 | |
| Cost of hospitalisation for severe herpes zoster_age group 13 | €5,064 | €4,051 | €6,077 | |
| Cost of hospitalisation for severe herpes zoster_age group 14 | €5,512 | €4,410 | €6,615 | |
| Cost of hospitalisation for severe herpes zoster_age group 15 | €5,344 | €4,275 | €6,413 | |
| Cost of hospitalisation for severe herpes zoster_age group 16 | €5,236 | €4,189 | €6,283 | |
| *Probability of productivity loss – varicella* | | | | |
| Probability of productivity loss for those with any varicella_age group 1 | 0% | 0% | 0% | Assumed no productivity loss because not of working age. |
| Probability of productivity loss for those with any varicella_age group 2 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 3 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 4 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 5 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 6 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 7 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 8 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any varicella_age group 9 | 28.5% | 25.7% | 31.4% | Central Statistics Office - labour force participation data.[175] Assumed lower and upper bounds +/-10%. |
| Probability of productivity loss for those with any varicella_age group 10 | 78.3% | 70.5% | 86.1% | |
| Probability of productivity loss for those with any varicella_age group 11 | 83.3% | 75.0% | 91.7% | |
| Probability of productivity loss for those with any varicella_age group 12 | 82.8% | 74.5% | 91.1% | |
| Probability of productivity loss for those with any varicella_age group 13 | 79.8% | 71.8% | 87.8% | |
| Probability of productivity loss for those with any varicella_age group 14 | 42.1% | 37.9% | 46.3% | |
| Probability of productivity loss for those with any varicella_age group 15 | 1.3% | 1.2% | 1.5% | |
| Probability of productivity loss for those with any varicella_age group 16 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 1 | 71.5% | 63.5% | 95.9% | Eurostat - EU-Statistics on Income and Living Conditions (EU-SILC) Instrument Ireland (2017-2021)[177] |
| Probability of productivity loss for carers of those with any varicella_age group 2 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 3 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 4 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 5 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 6 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 7 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 8 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any varicella_age group 9 | 0% | 0% | 0% | Assumed no caregiving required from 15 years of age. |
| Probability of productivity loss for carers of those with any varicella_age group 10 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 11 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 12 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 13 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 14 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 15 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any varicella_age group 16 | 0% | 0% | 0% | |
| *Probability of productivity loss - herpes zoster* | | | | |
| Probability of productivity loss for those with any herpes zoster_age group 1 | 0% | 0% | 0% | Assumed no productivity loss because not of working age. |
| Probability of productivity loss for those with any herpes zoster_age group 2 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any herpes zoster_age group 3 | 0% | 0% | 0% | |

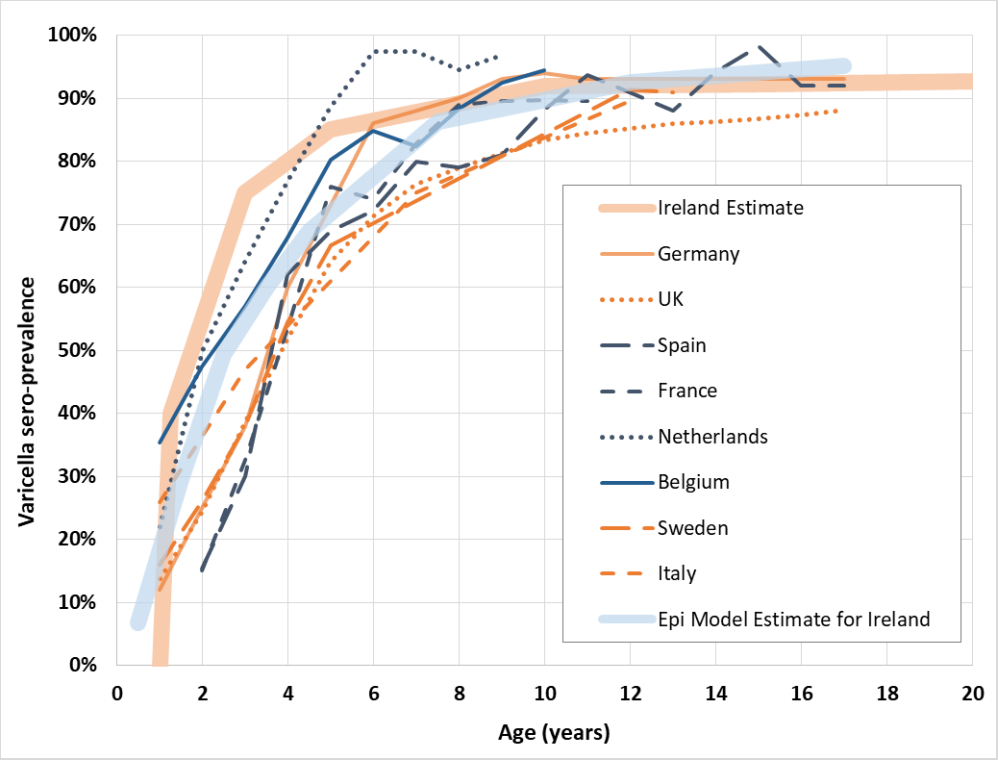
| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| Probability of productivity loss for those with any herpes zoster_age group 4 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any herpes zoster_age group 5 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any herpes zoster_age group 6 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any herpes zoster_age group 7 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any herpes zoster_age group 8 | 0% | 0% | 0% | |
| Probability of productivity loss for those with any herpes zoster_age group 9 | 28.5% | 25.7% | 31.4% | Central Statistics Office - labour force participation data.[175] Assumed lower and upper bounds +/-10%. |
| Probability of productivity loss for those with any herpes zoster_age group 10 | 78.3% | 70.5% | 86.1% | |
| Probability of productivity loss for those with any herpes zoster_age group 11 | 83.3% | 75.0% | 91.7% | |
| Probability of productivity loss for those with any herpes zoster_age group 12 | 82.8% | 74.5% | 91.1% | |
| Probability of productivity loss for those with any herpes zoster_age group 13 | 79.8% | 71.8% | 87.8% | |
| Probability of productivity loss for those with any herpes zoster_age group 14 | 42.1% | 37.9% | 46.3% | |
| Probability of productivity loss for those with any herpes zoster_age group 15 | 1.3% | 1.2% | 1.5% | |
| Probability of productivity loss for those with any herpes zoster_age group 16 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 1 | 0% | 0% | 0% | Assumed no productivity loss because not of working age. |
| Probability of productivity loss for those with PHN_age group 2 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 3 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 4 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 5 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 6 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 7 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 8 | 0% | 0% | 0% | |
| Probability of productivity loss for those with PHN_age group 9 | 28.5% | 25.7% | 31.4% | Central Statistics Office - labour force participation data.[175] Assumed lower and upper bounds +/-10%. |
| Probability of productivity loss for those with PHN_age group 10 | 78.3% | 70.5% | 86.1% | |
| Probability of productivity loss for those with PHN_age group 11 | 83.3% | 75.0% | 91.7% | |
| Probability of productivity loss for those with PHN_age group 12 | 82.8% | 74.5% | 91.1% | |
| Probability of productivity loss for those with PHN_age group 13 | 79.8% | 71.8% | 87.8% | |
| Probability of productivity loss for those with PHN_age group 14 | 42.1% | 37.9% | 46.3% | |
| Probability of productivity loss for those with PHN_age group 15 | 1.3% | 1.2% | 1.5% | |
| Probability of productivity loss for those with PHN_age group 16 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 1 | 71.5% | 63.5% | 95.9% | Eurostat - EU-Statistics on Income and Living Conditions (EU-SILC) Instrument Ireland (2017-2021)[177] |
| Probability of productivity loss for carers of those with any herpes zoster_age group 2 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 3 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 4 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 5 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 6 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 7 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 8 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 9 | 0% | 0% | 0% | Assumed no caregiving required from 15 years of age. |
| Probability of productivity loss for carers of those with any herpes zoster_age group 10 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 11 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 12 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 13 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 14 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 15 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with any herpes zoster_age group 16 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 1 | 71.5% | 63.5% | 95.9% | Eurostat - EU-Statistics on Income and Living Conditions (EU-SILC) Instrument Ireland (2017-2021)[177] |
| Probability of productivity loss for carers of those with PHN_age group 2 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with PHN_age group 3 | 71.5% | 63.5% | 95.9% | |

| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| Probability of productivity loss for carers of those with PHN_age group 4 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with PHN_age group 5 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with PHN_age group 6 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with PHN_age group 7 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with PHN_age group 8 | 71.5% | 63.5% | 95.9% | |
| Probability of productivity loss for carers of those with PHN_age group 9 | 0% | 0% | 0% | Assumed no caregiving required from 15 years of age. |
| Probability of productivity loss for carers of those with PHN_age group 10 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 11 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 12 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 13 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 14 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 15 | 0% | 0% | 0% | |
| Probability of productivity loss for carers of those with PHN_age group 16 | 0% | 0% | 0% | |
| *Indirect costs - productivity loss (1 day) for any varicella, herpes zoster and PHN* | | | | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 1 | €0.00 | €0.00 | €0.00 | Assumed no productivity loss because not of working age. |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 2 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 3 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 4 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 5 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 6 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 7 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 8 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 9 | €69.13 | €55.30 | €82.96 | Central Statistics Office – Earnings Analysis[176] Assumed lower and upper bounds +/-20%. |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 10 | €108.08 | €86.46 | €129.69 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 11 | €155.38 | €124.30 | €186.45 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 12 | €168.10 | €134.48 | €201.72 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 13 | €159.95 | €127.96 | €191.94 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 14 | €119.79 | €95.83 | €143.74 | |
| Productivity loss (1 day) for those with any varicella, herpes zoster and PHN_age group 15 | €119.79 | €95.83 | €143.74 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 1 | €143.85 | €108.08 | €168.10 | Central Statistics Office – Earnings Analysis[176] Assumed daily productivity loss for caregivers is the average of daily productivity loss for those aged 20-29years, 30-39years and 40-49years (that is, parents). Lower bound is set at daily productivity loss for 20-29year olds and upper bound is set at daily productivity loss for 40-49year olds. |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 2 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 3 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 4 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 5 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 6 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 7 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 8 | €143.85 | €108.08 | €168.10 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 9 | €0.00 | €0.00 | €0.00 | Assumed no caregiving required from 15 years of age. |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 10 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 11 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 12 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 13 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 14 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 15 | €0.00 | €0.00 | €0.00 | |
| Productivity loss (1 day) for caregivers of those with any varicella, herpes zoster and PHN_age group 16 | €0.00 | €0.00 | €0.00 | |
| *Work days lost* | | | | |
| Work days lost for those with non-severe varicella | 5 | 3 | 7 | Assumed work days lost equals infectious period of 7 days minus 2 weekend days. |
| Work days lost for those with non-severe herpes zoster | 5 | 3 | 7 | |

| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| Work days lost for those with PHN | 5 | 3 | 7 | Assumed the same as herpes zoster. |
| ***Note: work days lost for those with severe (hospitalised) varicella and severe (hospitalised) herpes zoster equals the number of work days lost for non-severe illness plus the (age-dependent) length of stay in hospital. | | | | |
| Work days lost for caregivers of those with non-severe varicella | 3 | 1 | 5 | Assumed based on non-published research. |
| Work days lost for caregivers of those with non-severe herpes zoster | 3 | 1 | 5 | Assumed based on non-published research. |
| Work days lost for caregivers of those with PHN | 3 | 1 | 5 | Assumed the same as herpes zoster. |
| ***Note: work days lost for those with severe (hospitalised) varicella and severe (hospitalised) herpes zoster equals the number of work days lost for non-severe illness plus the (age-dependent) length of stay in hospital. | | | | |
| *Length of stay – hospitalised case of varicella* | | | | |
| Average length of stay hospitalised varicella case_ age group 1 | 2.7 | 2.5 | 3.0 | Hospital Inpatient Enquiry (HIPE) System Discharge Data.[163] |
| Average length of stay hospitalised varicella case_ age group 2 | 2.6 | 2.2 | 2.9 | |
| Average length of stay hospitalised varicella case_ age group 3 | 2.6 | 2.2 | 2.9 | |
| Average length of stay hospitalised varicella case_ age group 4 | 3.4 | 2.2 | 5.4 | |
| Average length of stay hospitalised varicella case_ age group 5 | 3.5 | 2.6 | 4.3 | |
| Average length of stay hospitalised varicella case_ age group 6 | 2.8 | 2.0 | 4.0 | |
| Average length of stay hospitalised varicella case_ age group 7 | 3.2 | 2.9 | 4.1 | |
| Average length of stay hospitalised varicella case_ age group 8 | 4.0 | 2.6 | 5.5 | |
| Average length of stay hospitalised varicella case_ age group 9 | 4.0 | 2.6 | 5.5 | |
| Average length of stay hospitalised varicella case_ age group 10 | 6.6 | 2.8 | 13.2 | |
| Average length of stay hospitalised varicella case_ age group 11 | 6.6 | 2.8 | 13.2 | |
| Average length of stay hospitalised varicella case_ age group 12 | 9.1 | 5.6 | 18.7 | |
| Average length of stay hospitalised varicella case_ age group 13 | 9.1 | 5.6 | 18.7 | |
| Average length of stay hospitalised varicella case_ age group 14 | 15.7 | 13.8 | 19.2 | |
| Average length of stay hospitalised varicella case_ age group 15 | 15.7 | 13.8 | 19.2 | |
| Average length of stay hospitalised varicella case_ age group 16 | 13.3 | 12.2 | 14.7 | |
| *Length of stay - hospitalised case of herpes zoster* | | | | |
| Average length of stay hospitalised herpes zoster case_age group 1 | 3.4 | 2.7 | 4.5 | Hospital Inpatient Enquiry (HIPE) System Discharge Data.[163] |
| Average length of stay hospitalised herpes zoster case_age group 2 | 3.4 | 2.7 | 4.5 | |
| Average length of stay hospitalised herpes zoster case_age group 3 | 3.4 | 2.7 | 4.5 | |
| Average length of stay hospitalised herpes zoster case_age group 4 | 3.4 | 2.7 | 4.5 | |
| Average length of stay hospitalised herpes zoster case_age group 5 | 3.4 | 2.7 | 4.5 | |
| Average length of stay hospitalised herpes zoster case_age group 6 | 3.4 | 2.7 | 4.5 | |
| Average length of stay hospitalised herpes zoster case_age group 7 | 3.4 | 2.7 | 4.5 | |
| Average length of stay hospitalised herpes zoster case_age group 8 | 3.8 | 3.3 | 4.6 | |
| Average length of stay hospitalised herpes zoster case_age group 9 | 3.8 | 3.3 | 4.6 | |
| Average length of stay hospitalised herpes zoster case_age group 10 | 3.5 | 2.4 | 4.6 | |
| Average length of stay hospitalised herpes zoster case_age group 11 | 3.3 | 1.9 | 5.7 | |
| Average length of stay hospitalised herpes zoster case_age group 12 | 7.1 | 2.4 | 17.1 | |
| Average length of stay hospitalised herpes zoster case_age group 13 | 4.2 | 3.2 | 5.7 | |
| Average length of stay hospitalised herpes zoster case_age group 14 | 4.8 | 3.9 | 5.3 | |
| Average length of stay hospitalised herpes zoster case_age group 15 | 9.8 | 6.0 | 16.9 | |
| Average length of stay hospitalised herpes zoster case_age group 16 | 12.6 | 10.3 | 15.7 | |
| *Quality adjusted life year (QALY) loss* | | | | |
| QALY loss varicella_age group 1-8 | 0.0040 | 0.0032 | 0.0048 | Brisson et al.[165] |
| QALY loss varicella_age group 9-16 | 0.0050 | 0.0040 | 0.0060 | |
| QALY loss breakthrough varicella_all age groups | 0.0010 | 0.0008 | 0.0012 | |
| QALY loss acute herpes zoster_age groups 1-14 | 0.0100 | 0.0060 | 0.0160 | Pellesier et al.[166] |
| QALY loss acute herpes zoster_age groups 15-16 | 0.0120 | 0.0070 | 0.0180 | |

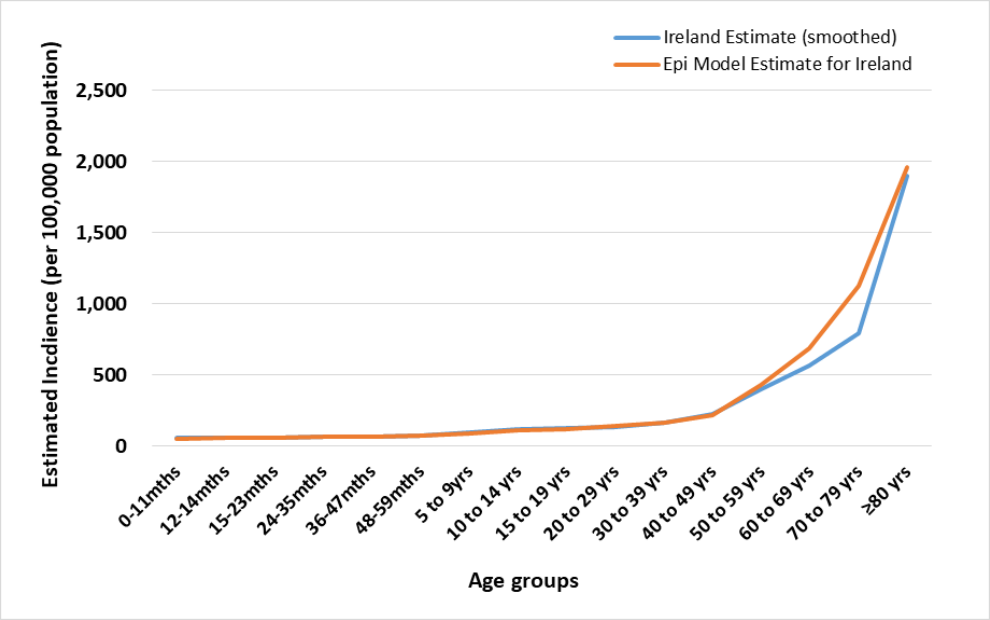
| Parameter Description | Base case value | Lower bound | Upper bound | Source |
|---|---|---|---|---|
| QALY loss PHN_age groups 1-14 | 0.1060 | 0.0680 | 0.1620 | |
| QALY loss PHN_age groups 15-16 | 0.1560 | 0.1000 | 0.2330 | |
| QALY loss herpes zoster after varicella vaccination_1-14 | 0.0100 | 0.0060 | 0.0160 | Assumed the same as herpes zoster. |
| QALY loss herpes zoster after varicella vaccination _15-16 | 0.0120 | 0.0070 | 0.0180 | |
| *Varicella vaccination programme parameters* | | | | |
| Eligible population for budget impact analysis | 60,000 | 60,000 | 60,000 | Central Statistics Office[2] |
| Coverage 1st dose | 88.0% | 83.1% | 93.0% | Health Protection Surveillance Centre[151] (Average immunisation uptake rate [12 vaccines] in children 24months of age Q3 2022). |
| Coverage 2nd dose | 87.9% | 83.0% | 92.9% | Health Protection Surveillance Centre[151, 152] (Average immunisation uptake rate [12 vaccines] in children 24months of age Q3 2022 and those in Junior Infants 2020-2021). |
| Coverage target | 95.0% | 95.0% | 95.0% | Health Service Executive[239] |
| Cost of varicella vaccine - dose one | €32.73 | €26.18 | €39.28 | Akpo et al.[132] (€ equivalent of average of monovalent prices used). Assumed lower and upper bound +/-20%. |
| Cost of varicella vaccine - dose two | €32.73 | €26.18 | €39.28 | Assumed the same as dose one. |
| Cost of vaccine administration by GPs (per dose) | €19.73 | €15.78 | €23.68 | Calculated based on current fees paid to GPs for administering childhood vaccines in Ireland.[178] Assumed lower and upper bound +/-20%. |
| Cost of vaccine administration by the HSE (per dose) | €19.73 | €15.78 | €23.68 | Assumed equal to GP payment for vaccine administration. |
| Cold chain service cost as a proportion of vaccine procurement cost | 3.9% | 2.2% | 6.5% | Health Service Executive.[179] |
| Education and Communication cost as a proportion of vaccine procurement cost | 1.5% | 40.0% | 4.4% | |
| VAT | 23% | 23% | 23% | Revenue Irish Tax and Customs.[240] |
| Probability of mild adverse event with varicella vaccine | 27.0% | 10.0% | 50.0% | WHO.[164] Assumed to be mild adverse event with greatest probability of occurrence (Fever MMRV vaccine). Assumed lower and upper bound. |
| QALY loss vaccination mild adverse events | 0.00010 | 0.00005 | 0.00015 | In the absence of data, assumed utility decrement (0.04) is half that of breakthrough varicella and lasts for one day. |
| *Discount rates* | | | | |
| Annual discount rate - costs (%) | 4.0% | 0.0% | 10.0% | Health Information and Quality Authority.[139] |
| Annual discount rate - outcomes (%) | 4.0% | 0.0% | 10.0% | |

## Appendix A7.4a Estimated varicella sero-prevalence in Europe and epidemiological model estimate of varicella sero-prevalence in Ireland (before universal childhood vaccination)†




†**Sources:** Ireland,[45, 144] Germany,[241] UK,[242] Spain,[243] France,[244] the Netherlands,[245] Belgium,[246] Sweden,[247] Italy[248]

## Appendix A7.4b Estimated incidence of herpes zoster and epidemiological model estimate of incidence of herpes zoster in Ireland (before universal childhood vaccination)†




†**Sources:** Ireland[143] and see section 7.2.6.

# Appendix A7.5 Costs incurred and costs averted for budget impact analysis of varicella vaccination

| Year | Costs Incurred | Vaccination Strategy | | | Costs Averted | Vaccination Strategy | | |
|---|---|---|---|---|---|---|---|---|
| | **Cost item** | **1 dose** | **2 dose (SI)** | **2 dose (LI)** | **Cost item** | **1 dose** | **2 dose (SI)** | **2 dose (LI)** |
| **Year 1** | Vaccine procurement | 2,125,617 | 3,719,830 | 2,125,617 | GMS scheme medication for HZ | -84 | -85 | -84 |
| | Vaccine administration | 1,041,744 | 1,823,052 | 1,040,264 | GMS scheme medication for PHN | -3 | -3 | -3 |
| | Cold storage, transportation | 82,899 | 145,073 | 82,781 | Hospitalisation with varicella | -722,098 | -750,814 | -700,975 |
| | Education and Communication | 31,884 | 55,797 | 31,839 | Hospitalisation with HZ | -119 | -120 | -119 |
| | **Total Cost Incurred Year 1** | **3,282,144** | **5,743,753** | **3,277,482** | **Total Cost Averted Year 1** | **-722,304** | **-751,021** | **-701,182** |
| | | | | | | | | |
| **Year 2** | Vaccine procurement | 2,125,617 | 4,251,234 | 2,125,617 | GMS scheme medication for HZ | -620 | -625 | -620 |
| | Vaccine administration | 1,041,744 | 2,083,488 | 1,041,744 | GMS scheme medication for PHN | -23 | -24 | -23 |
| | Cold storage, transportation | 82,899 | 165,798 | 82,899 | Hospitalisation with varicella | -659,895 | -732,367 | -684,266 |
| | Education and Communication | 31,884 | 63,769 | 31,884 | Hospitalisation with HZ | -813 | -817 | -813 |
| | **Total Cost Incurred Year 2** | **3,282,144** | **6,564,289** | **3,282,144** | **Total Cost Averted Year 2** | **-661,352** | **-733,832** | **-685,722** |
| | | | | | | | | |
| **Year 3** | Vaccine procurement | 2,125,617 | 4,251,234 | 2,125,617 | GMS scheme medication for HZ | -1,412 | -1,436 | -1,413 |
| | Vaccine administration | 1,041,744 | 2,083,488 | 1,041,744 | GMS scheme medication for PHN | -57 | -58 | -57 |
| | Cold storage, transportation | 82,899 | 165,798 | 82,899 | Hospitalisation with varicella | -594,433 | -709,984 | -663,535 |
| | Education and Communication | 31,884 | 63,769 | 31,884 | Hospitalisation with HZ | -1,699 | -1,724 | -1,700 |
| | **Total Cost Incurred Year 3** | **3,282,144** | **6,564,289** | **3,282,144** | **Total Cost Averted Year 3** | **-597,600** | **-713,202** | **-666,705** |
| | | | | | | | | |
| **Year 4** | Vaccine procurement | 2,125,617 | 4,251,234 | 2,125,617 | GMS scheme medication for HZ | -2,126 | -2,275 | -2,161 |
| | Vaccine administration | 1,041,744 | 2,083,488 | 1,041,744 | GMS scheme medication for PHN | -91 | -97 | -92 |
| | Cold storage, transportation | 82,899 | 165,798 | 82,899 | Hospitalisation with varicella | -670,645 | -827,719 | -782,729 |
| | Education and Communication | 31,884 | 63,769 | 31,884 | Hospitalisation with HZ | -2,363 | -2,507 | -2,397 |
| | **Total Cost Incurred Year 4** | **3,282,144** | **6,564,289** | **3,282,144** | **Total Cost Averted Year 4** | **-675,224** | **-832,598** | **-787,378** |
| | | | | | | | | |
| **Year 5** | Vaccine procurement | 2,125,617 | 4,251,234 | 4,251,234 | GMS scheme medication for HZ | -2,633 | -2,983 | -2,754 |
| | Vaccine administration | 1,041,744 | 2,083,488 | 2,083,488 | GMS scheme medication for PHN | -115 | -132 | -121 |
| | Cold storage, transportation | 82,899 | 165,798 | 165,798 | Hospitalisation with varicella | -633,406 | -829,393 | -785,547 |
| | Education and Communication | 31,884 | 63,769 | 63,769 | Hospitalisation with HZ | -2,766 | -3,063 | -2,867 |
| | **Total Cost Incurred Year 5** | **3,282,144** | **6,564,289** | **6,564,289** | **Total Cost Averted Year 5** | **-638,920** | **-835,571** | **-791,290** |
| | | | | | | | | |
| **Years 1-5** | Vaccine procurement | 10,628,086 | 20,724,767 | 12,753,703 | GMS scheme medication for HZ | -6,875 | -7,403 | -7,033 |
| | Vaccine administration | 5,208,720 | 10,157,004 | 6,250,464 | GMS scheme medication for PHN | -289 | -314 | -297 |
| | Cold storage, transportation | 414,495 | 808,266 | 497,394 | Hospitalisation with varicella | -3,280,476 | -3,850,277 | -3,617,052 |
| | Education and Communication | 159,421 | 310,872 | 191,306 | Hospitalisation with HZ | -7,760 | -8,230 | -7,896 |
| | **Total Cost Incurred Years 1-5** | **16,410,722** | **32,000,908** | **19,692,867** | **Total Cost Averted Years 1-5** | **-3,295,401** | **-3,866,224** | **-3,632,278** |

**Key:** GMS – General Medical Services; HZ – herpes zoster; LI – long interval; PHN – post herpetic neuralgia; SI – short interval

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