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Childhood varicella vaccination: an evaluation of clinical effectiveness, safety and cost effectiveness in Ireland

Thesis presented by
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2024

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Thesis declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

Signed: 

Student Number: 94373655

Date: 18 September 2024

List of abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BV	breakthrough varicella
CCA	corrected covered area
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CIDR	computerised infectious disease reporting
CPI	consumer price index
CSO	Central Statistics Office
CUA	cost-utility analysis
DAM	decision analytical modelling
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis
EEA	European Economic Area
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EU-SILC	European Union – Statistics on Income and Living Conditions
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HPO	Healthcare Pricing Office
HPSC	Health Protection Surveillance Centre
HTA	health technology assessment
HZ	herpes zoster
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
iGAS	invasive Group A streptococcus
LOS	length of stay
MMR	measles mumps rubella

MMRV	measles mumps rubella varicella
OTC	over-the-counter
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
SORT	Strength of Recommendation Taxonomy
SR	systematic review
UVV	universal varicella vaccination
VE	vaccine effectiveness
VZV	varicella zoster virus
WHO	World Health Organization
WTP	willingness-to-pay

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Thesis abstract

Background

Varicella (chickenpox) is a common, highly contagious, vaccine-preventable disease that mainly affects children. Although typically mild, serious complications requiring hospitalisation do occur. Varicella is also associated with significant productivity loss mainly due to absence from paid work for those caring for people who are sick with the disease. While 44 countries and regions globally recommend childhood varicella vaccination, recommendations differ between countries. Currently varicella vaccination is not offered as part of the routine childhood immunisation schedule in Ireland.

Aim

The overall aim of this thesis was to analyse the clinical effectiveness and safety of childhood varicella vaccination and the cost effectiveness of universal childhood varicella vaccination in Ireland. In doing so, it sought to help inform a public health policy decision regarding the addition of varicella vaccination to the childhood immunisation schedule in Ireland.

Methods

This thesis applied the analytical tools of systematic review and economic evaluation across four inter-related studies. Two overviews of systematic reviews were conducted to synthesise the international evidence on the clinical effectiveness (study 1) and safety (study 2) of childhood varicella vaccination. To 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 economic modelling studies was undertaken (study 3). Lastly, a cost-utility analysis (CUA) was conducted to estimate the cost effectiveness of universal childhood varicella vaccination in Ireland (study 4).

Results

From a total of 20 systematic reviews, there was clear and consistent evidence that vaccination is very effective at reducing varicella. The evidence suggests that two-dose strategies are more effective than one-dose strategies in preventing varicella of any severity, but that both strategies have similarly high effectiveness in preventing moderate or severe varicella. From a total of 17 systematic reviews, the evidence suggests that mild local and systemic reactions are relatively common with varicella vaccination, and serious adverse reactions are rare.

The rapid review of economic modelling studies identified a number of important structural features and input parameter data that were incorporated into the dynamic transmission model of varicella zoster virus developed for Ireland. Based on the CUA, it was found that from the perspective of the publicly funded healthcare system, a one-dose varicella vaccination strategy would be cost effective compared with no vaccination, with an incremental cost-effectiveness ratio (ICER) of €8,700 per quality-adjusted life year (QALY) gained. Relative to a one-dose strategy, a two-dose strategy would be less cost effective with an ICER of approximately €45,000 per QALY gained, with little difference in the cost effectiveness of a two-dose short interval and a two-dose long interval strategy. From a societal perspective, both one- and two-dose vaccination strategies would be cost saving compared with no vaccination, with the two-dose short interval strategy dominant, being the least costly and most effective. The results of the CUA were robust to both sensitivity and scenario analyses.

Conclusion

The current evidence suggests that varicella vaccination is safe and highly effective in preventing varicella in children. While both one- and two-dose strategies are effective in preventing severe disease, a two-dose strategy is more effective in preventing varicella (cases and outbreaks). From a societal perspective, universal childhood varicella vaccination would be cost saving in Ireland. From the payer perspective, a one-dose strategy would be highly cost effective and sufficient to

reduce severe morbidity from varicella. However, a two-dose strategy would be required to potentially achieve elimination of the disease. A policy decision to add the varicella vaccine to the childhood immunisation schedule in Ireland should consider the totality of the evidence presented in this thesis in the context of the stated aim of such a programme, that is, whether the aim is to reduce incidence of severe disease or eliminate varicella. Additionally, a decision to add another vaccine to the childhood immunisation schedule should consider relevant organisational, social and ethical issues.

Research outputs

Peer-reviewed publications

- **Ahern S**, Walsh KA, Paone S, Browne J, Carrigan M, Harrington P, Murphy A, Teljeur C, Ryan M. Clinical efficacy and effectiveness of alternative varicella vaccination strategies: An overview of reviews. **Reviews in Medical Virology**. 2023 Jan;33(1):e2407. doi: 10.1002/rmv.2407.
    - **Shortlisted in the Public Health Medicine and Epidemiology category at the 2022 Royal Academy of Medicine in Ireland (RAMI) Research Awards.**
- **Ahern S**, Walsh KA, Paone S, Browne J, Carrigan M, Harrington P, Murphy A, Teljeur C, Ryan M. Safety of varicella vaccination strategies: An overview of reviews. **Reviews in Medical Virology**. 2023 Mar;33(2):e2416. doi: 10.1002/rmv.2416.
- **Ahern S**, Browne J, Murphy A, Teljeur C, Ryan M. An economic evaluation and incremental analysis of the cost effectiveness of three universal childhood varicella vaccination strategies for Ireland. **Vaccine.** 2024; 42(14). doi.org/10.1016/j.vaccine.2024.04.027.

Oral presentations

- **Ahern S**, Walsh KA, Paone S, et al. An Overview of reviews of the Clinical Effectiveness and Safety of Varicella (chickenpox) Vaccination. SPHeRE Network 9th Annual Conference 2023. Dublin, Ireland. 23 March 2023.
- **Ahern S**, Murphy A, Ryan M, Teljeur C. Universal childhood varicella (chickenpox) vaccination in Ireland: a cost-utility analysis. Cork University Business School Postgraduate Research Symposium 2023. Cork, Ireland. 29 June 2023.
- **Ahern S,** Walsh KA, Paone S, Harrington P, Teljeur C, Ryan M. Universal childhood varicella (chickenpox) vaccination in Ireland: a health technology assessment. SPHeRE Network 10th Annual Conference 2024. Dublin, Ireland. 29 February 2024.

Poster presentations

- **Ahern S**, Carrigan M, Harrington P. et al. A rapid review of economic models of childhood varicella vaccination. SPHeRE Network 9th Annual Conference 2023. Dublin, Ireland. 23 March 2023.

- **Ahern S**, Murphy A, Ryan M, Teljeur C. An economic evaluation of universal childhood varicella vaccination in Ireland. ISPOR Europe 2023. Copenhagen, Denmark. 12 to 15 November 2023.

- **Ahern S**, Teljeur C, Ryan M. How Many Simulations of a Dynamic Transmission Model Are Enough to Estimate Uncertainty? ISPOR Europe 2023. Copenhagen, Denmark. 12 to 15 November 2023.

Published abstracts

- **Ahern S**, Teljeur C, Murphy A, Ryan M. EE442 An Economic Evaluation of Universal Childhood Varicella Vaccination in Ireland. **Value in Health**. 2023 Dec 1;26(12):S136. doi: 10.1016/j.jval.2023.09.708.

- **Ahern S**, Teljeur C, Ryan M. MSR87 How Many Simulations of a Dynamic Transmission Model Are Enough to Estimate Uncertainty? **Value in Health**. 2023 Dec 1;26(12):S409. doi: 10.1016/j.jval.2023.09.2146.

Published protocol

- **Ahern S**, Walsh KA, Browne J, Harrington P, Murphy A, Teljeur C, Ryan M. Clinical efficacy, effectiveness and safety of alternative varicella vaccination strategies: an overview of reviews. **PROSPERO** 2022 CRD42022312325 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022312325

Health technology assessment reports

- Health Information and Quality Authority. Expansion of the childhood immunisation schedule to include varicella (chickenpox) vaccination. Protocol for a Health Technology Assessment. 2022. Available from: HTA_Protocol_Varicella_Vaccination (hiqa.ie)

- Health Information and Quality Authority. Health Technology Assessment of Expansion of the childhood immunisation schedule to include varicella (chickenpox) vaccination. 2023. Available from: HTA_Report_Varicella_Vaccination (hiqa.ie)

- Health Information and Quality Authority. Report on the results of the public consultation on the Health Technology Assessment of the expansion of the childhood immunisation schedule to include varicella (chickenpox) vaccination. 2023 Available from: Statement of Outcomes_Report (hiqa.ie)

1 Introduction

1.1 Rationale, aims and objectives of this thesis

As the bodies of evidence to support public health interventions continue to grow, the demands on public health budgets are ever increasing. Against a backdrop of finite resources for public health, the process of making policy choices and allocating resources between interventions has become increasingly complex. Since the late 1990s, evidence-based public health has thus been advocated to inform decision-making regarding the most effective and efficient use of limited public health resources.[1-4]

This thesis aims to help inform a public health policy decision regarding the addition of varicella vaccination to the childhood immunisation schedule in Ireland by conducting a comprehensive evidence synthesis, including an economic analysis, to enable evidence-based decision making. In doing so, this thesis draws on the theory and empirical work that underpins applied research methodology in the areas of both evidence synthesis and health economics and specifically applies the evidence-based public health analytical tools of systematic review and economic evaluation.

The importance of ongoing surveillance and monitoring of the safety and effectiveness of vaccines is widely recognised by those agencies responsible for authorisation, with processes and systems for monitoring clearly defined.[5-7] Since universal childhood varicella vaccination was first introduced in the United States in the 1990s, a growing body of evidence has been published on both the effectiveness and safety of varicella vaccines. This evidence reflects the evolution of childhood varicella vaccination strategies since the development of the vaccine almost 50 years ago and the different strategies offered in countries with established childhood varicella immunisation programmes. While numerous systematic reviews have been published to date, no existing review captures the effectiveness and safety of the range of possible varicella vaccination strategies. Additionally, to the best of my knowledge, an economic evaluation of universal childhood varicella vaccination for Ireland has not yet been conducted.

This thesis seeks to answer the following research questions:

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

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

- What approaches have been used to model the expected costs and benefits of childhood varicella vaccination?

- Is universal childhood varicella vaccination cost effective in Ireland?

To address these questions, this introductory chapter includes a description of the international evidence on the epidemiology of varicella. It also sets out the impact of varicella on health outcomes and health service utilisation, as well as broader societal impacts such as absence from the workplace. Specific issues of relevance in the Irish context are also described. Lastly, an overview of the methodologies used to address the research questions posed above is provided.

1.2 Overview of varicella

Varicella (chickenpox) is a common, highly contagious, vaccine-preventable disease that occurs worldwide and mainly affects children. Primary infection with the varicella-zoster virus (VZV) 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 (shingles). Varicella is characterised by a fever and pruritic, blister-like rash, mostly on the face and torso, typically lasting four to seven days.[8] Transmission of VZV from person to person mainly occurs by direct contact with the varicella or herpes zoster rash or inhalation of aerosolized droplets from respiratory secretions of those with varicella. After initial VZV infection, most people develop immunity to varicella for the remainder of their lives, with recurrent varicella very rare.[9]

The epidemiology of varicella differs in temperate and tropical climates. In the absence of routine vaccination, incidence of varicella in temperate climates ranges

from 13 to 16 cases per 1,000 population per year.[10, 11] Age-specific varicella incidence is highest in early childhood. As a result, approximately 90% of people have been infected with the disease before adolescence, with less than 10% of people susceptible as adults.[12] In tropical climates, varicella is common in adolescents and the proportion of cases observed in adults is higher than in temperate climates.[11, 13] Within Europe, while there are many similarities in the epidemiology of varicella, there are also some differences reported in sero-epidemiology studies with seroconversion at a younger age in Northern and Western Europe, compared with Eastern and Southern Europe.[14-16] These differences may relate to both earlier socialisation in the community in some countries, where greater numbers of children attend childcare facilities at a younger age, and different urbanisation patterns between countries.[14]

While typically a mild disease, varicella can lead to serious complications. Those at increased risk of complications include infants, adults, pregnant women and those with compromised immune function.[8, 12] The most frequent complications are severe disease, skin-related complications including long-term skin scarring, and secondary infection-related complications.[17] Based on limited data reported, the prevalence of skin scarring may range from 12% to 19%, with the number and location of scars varying considerably among cases.[18, 19] Serious complications associated with varicella 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.[20] In addition to its association with bacterial superinfection of skin lesions, varicella is a neurotropic virus and it is recognised as being associated with stroke in both children and adults.[21]

The annual global disease burden of varicella has been conservatively estimated to include 4.2 million complications requiring hospitalisation and 4,200 deaths.[13, 22] Additionally, there is a significant societal and economic burden associated with varicella, mainly due to the high number of cases in children each year and the resulting need for parents and caregivers to take time off paid employment to care

for those who are ill.[23] In Europe, the indirect costs associated with lost productivity due to varicella have been estimated at €433 million, accounting for approximately two-thirds of the total costs associated with the disease.[24, 25]

1.3 Varicella in Europe

Varicella occurs worldwide and although it is typically recognised as a disease of childhood, serological evidence of past exposure to VZV in adults suggests that adults are more susceptible in tropical and sub-tropical countries.[10, 11, 13] Given that the intervention being assessed in the course of this research specifically relates to children, the epidemiology of varicella in Europe, as a temperate region, is described below.

1.3.1 Epidemiology

1.3.1.1 Incidence and seroprevalence in children

In Europe, and in the absence of universal vaccination, the number of varicella cases in a country is approximately the same as the birth cohort.[20] In Ireland, the total number of births in 2023 was c. 55,000.[26]

In a European study that included 16 countries, estimated annual incidence of varicella (derived from seroprevalence data published between 1995 and 2016) was highest in those under five years of age in 13 countries.[27] In Greece, Italy and Switzerland, the highest incidence of varicella was reported in the five to nine year old age group.[27] Across Europe, annual incidence ranged from 7,052 (Greece) to 16,122 cases (the Netherlands) per 100,000 population in the age group less than five years old, from 3,292 (Luxembourg) to 11,798 cases (Switzerland) per 100,000 population in five to nine year old age group, and from 20 (the Netherlands) to 2,804 cases (Greece) per 100,000 population in the 10 to 14 year old age group.[27] In Ireland, the annual incidence rate of VZV primary infection was estimated at 11,954 per 100,000 population for those aged less than five years, 6,434 per 100,000 population for those aged five to nine years and falling to 76 per 100,000 population for those aged 10 to 14 years.[27]

The first international study that compared the standardised pre-vaccination serology of VZV in the European region (11 countries including Ireland with testing between 1996 and 2003), reported that across all participating countries, with the exception of Italy, over 50% of young children had antibodies to VZV by 5 years of age, 70% by nine years of age, and 90% by 14 years of age.[16] In Italy, 38% of children were seropositive at age five, 61% at age nine years, and 82% at age 14 years.[16] In Ireland, 82% of children in Ireland had antibodies to VZV by nine years of age and 92% by 14 years of age.[16] In a subsequent review of sero-epidemiology studies of antibodies against varicella conducted in Europe between 2004 and 2014, at least 90% of individuals tested were seropositive by 12 years of age in Finland, France, Luxembourg, the Netherlands, Slovenia, and Sweden.[14] A systematic review of seroprevalence studies published between 1995 and 2016 in Europe, that also used data collected before the introduction of universal vaccination, estimated the seroprevalence rate in those aged less than 10 years ranged from 72.6% in Greece to 97.4% in the Netherlands.[27] In Ireland, the seroprevalence rate was estimated at 91.9%.[27]

As only hospitalised cases of varicella disease are notifiable in Ireland, incidence is monitored through a sentinel general practice surveillance programme.[28] In 2019 (the most recent non-COVID-19 year for which data are available), 87% of varicella notifications from sentinel general practice sites related to children aged less than nine years of age.[29]

1.3.1.2 Incidence in adults

While varicella is typically a childhood illness, it also affects adults. It is often more severe in adults than children, with complications also more common.[30] In a European study that estimated incidence of varicella in adults from seroprevalence data available before universal varicella vaccination, estimates varied considerably between countries. They ranged from 18 (the Netherlands) to 371 cases (Italy) per 100,000 population in the 20 to 39 year old age group and from 9 (Poland) to 112 cases (Italy) per 100,000 population in 40 to 64 year old age group.[27] The annual incidence rate of VZV primary infection in adults in Ireland was 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.[27] Based on data from the sentinel general practices in Ireland from 2005 to 2019 inclusive, adults aged at least 20 years represented 5% (2014) to 14% (2005) of all varicella notifications.[29] For 2019, the most recent year for which data are available and that was not impacted by COVID-19, 7% of all varicella notifications from sentinel general practices in Ireland related to adults aged 20 years and older.[29]

The first international study that compared the standardised pre-vaccination serology of VZV in the European region (11 countries including Ireland with testing between 1996 and 2003), reported that all countries included in the study reported seropositivity in excess of 90% by 29 years of age, with the exception of Italy (89%).[16] In Ireland, 94% of adults had antibodies to VZV by 29 years of age.[16] In a subsequent study covering a wider period from 1995 to 2016, estimates of the seroprevalence rate by 19 years of age also exceeded 90% in all 16 European countries included, with the exception of Italy (89%).[27]

1.3.1.3 Incidence in pregnant women

While a significant proportion of women, including those in Ireland, will have had varicella many years before becoming pregnant, varicella is estimated to cause complications in approximately 0.5 to 3 of every 1,000 pregnancies globally.[31-33] Increased morbidity and mortality has been reported in pregnant women who develop varicella, with pneumonia occurring in approximately 10-20% of cases.[33-36] Varicella may cause severe disease in susceptible pregnant women (primarily pneumonia), foetal death or congenital varicella syndrome, characterised by limb hypoplasia, cutaneous scarring, and ocular and central nervous system abnormalities. Risks to the foetus and neonate are related to the timing of maternal infection.[37, 38] 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.[38, 39] 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).[38] 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.[38]

1.3.2 Burden of disease

1.3.2.1 General practitioner attendance

A recent systematic review reported that primary care use for varicella differs greatly between countries, with the proportion of patients attending primary care ranging from 40% to almost 100% and the average number of primary care visits per episode ranging from 0.04 to 2.2.[25] A study estimating the overall burden of varicella in Europe before the introduction of universal varicella vaccination, estimated that 54% of all varicella cases in Europe lead to a physician consultation.[40] In the same study, there was substantial variation between countries in Europe and while estimates were consistently highest in children aged less than five years, they ranged from 1,100 per 100,000 in Romania to 13,069 per 100,000 in France.[40] Estimates of annual primary care incidence for varicella for Ireland ranged from 6,349 to 7,080 per 100,000 population in those aged less than five years and from 2,768 to 3,878 per 100,000 population in those aged five to nine years.[40] 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 healthcare seeking behaviour, and therefore primary care utilisation rates, vary considerably between countries.[40] Additionally, the availability of and barriers to accessing primary care also differ between European countries leading to differences in healthcare seeking behaviour.

A UK study analysed general practice records from more than eight million people over a 10 year period from 2005 to 2014, and reported data on the burden of varicella on UK general practice.[41] For each year of the study period, estimated annual consultation rates were highest among those aged one to three years, ranging from 61.2 consultations per 1,000 person-years in 2007 to 39.7 per 1,000 person-years in

2014.[41] Overall, consultation rates fell with increasing age; the rates in those aged over 20 years were less than one varicella consultation per 1,000 person-years throughout the study period.[41] Similarly, a retrospective population-based cohort study from the Netherlands that included 165,000 patients, reported that the highest incidence of varicella general practitioner (GP) consultations was found in the one to four year old age group at 610.8 per 10,000 population.[42] Data on overall GP attendance due to varicella in Ireland are not available, other than from the sentinel general practice surveillance data highlighted above in Section 1.3.1.1.

1.3.2.2 Hospitalisation and complications

Unlike primary care resource use, hospitalisation patterns for varicella are not dissimilar across countries and regions. Overall, it is reported that less than 1% of patients with varicella require hospitalisation, with the risk highest in infants less than one year old and adults.[11, 25, 40] However, most hospitalisations do occur in otherwise healthy children.[11, 43]

Using hospital registry data from 2000 to 2007, the annual incidence of hospitalisation for varicella in Belgium was estimated at 5.3 admissions per 100,000 person-years.[44] The hospitalisation rate was highest for children aged less than two years, at between 110 (females) and 140 (males) admissions per 100,000 population. Of the hospitalised varicella cases, 40 to 45% had no complication, 10 to 15% had a mild skin infection and another 10 to 15% had an acute comorbidity which may have been the primary reason for hospitalisation. Based on hospital inpatient care data from the National Patient Register in Sweden, covering the period from 2007 to 2013, the hospitalisation rate for varicella in Sweden was estimated at 3.6 admissions per 100,000 person-years.[45] The hospitalisation rate was highest in those aged one year (41.0 admissions per 100,000 person-years).

Using the Hospital Episode Statistics database for NHS hospitals for the period 2004 to 2013, the annual incidence of hospitalisation for varicella in England was estimated at 7.6 admissions per 100,000 population, with the immunocompetent population accounting for 93% of admissions.[46] The highest incidence of

hospitalisation due to varicella was recorded in the age group less than 10 years old, with 51 admissions per 100,000 population. A subsequent study, conducted from 2004 to 2017, reported an estimated annual incidence rate of 8.9 admissions per 100,000 population.[47] The highest incidence of hospitalisation due to varicella was recorded in the younger age groups at 139 per 100,000 population in the group less than one year old and 87 per 100,000 population in the age group from one to four years old. 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.[47] 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%).[47]

In Ireland, the 1981 Infectious Disease Regulations and subsequent amendments, identify a range of notifiable infectious diseases.[48] 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 or Director of Public Health 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. The number of notifiable hospitalised cases of varicella varies considerably from year to year. In 2018, a total of 99 notifiable cases were reported, representing a crude incidence rate of 2.1 cases per 100,000 population. The highest age specific incidence rate of notifiable cases was reported in those aged less than one year and estimated at 30.5 cases per 100,000 population.[49] In 2019, a total of 93 notifiable hospitalised cases were notified.[50] However, due to the impact of the COVID-19 pandemic, the 2019 Annual Epidemiology Report for varicella (hospitalised cases) which includes further detail on cases, was not published.

Based on data from the National Notifiable Disease Hub database, which reports notifiable hospitalised cases of varicella in Ireland over a rolling five-year period, a total of 75 hospitalised cases of varicella were notified to the HPSC in 2022 and 170 in 2023.[51] Data on notifiable hospitalisations from 2020 and 2021 illustrate the likely impact that non-pharmaceutical interventions to prevent SARS-CoV-2 transmission

during COVID-19 pandemic, had on typical VZV transmission. The number of notifiable hospitalised cases of varicella for the last 10 years and by age group for the last five years (2024 case numbers are up to week 25) are presented in **Table 1.1**.

Table 1.1 Notifiable hospitalised varicella cases in Ireland by year and age group

Year	0-4yrs	5-12yrs	13-18yrs	19-24yrs	25-44yrs	45-64yrs	≥65yrs	Total
2024*	15	15	1	4	9	4	8	51
2023	76	37	9	5	22	7	14	170
2022	10	7	2	7	24	11	14	75
2021	4	9	1	0	5	2	2	23
2020	7	8	1	0	2	3	4	25
2019	Not available							93
2018	Not available							99
2017	Not available							105
2016	Not available							106
2015	Not available							69

*2024 case numbers are up to week 25.
Source: Annual Epidemiological Report 2019[49] and National Notifiable Disease Hub[51]

Data from the Hospital In-Patient Enquiry system (HIPE), the principal source of national discharge data from acute hospitals in Ireland, have also been used to examine hospital admissions for patients with primary varicella infection.[52] 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.[52] Infants and young children comprised the majority of admissions; 47% were less than three years old and 76% were less than 10 years old.[52] 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.[52] A total of 757 (28%) admissions had a complicating diagnosis, the most common being cellulitis, volume depletion and streptococcal infection.[52] 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

varicella accounted for an average of 1,130 acute hospital and 161 ICU bed days annually over the study period.[52]

The difference between notified and HIPE cases of varicella-related hospitalisations in Ireland 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.[46, 53] As with the data from the HPSC, there is potential for under-reporting of varicella cases in the HIPE system as the episode of care for those presenting with complications of varicella may not be coded correctly. Therefore, the rate of hospitalisation reported from HIPE may also be an under-estimate of the true rate. However, given that the incidence of varicella-related hospitalisation in Ireland is consistent with that in countries without universal varicella vaccination, it suggests that if there is under-reporting, it is likely to be limited.

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.[54, 55] A number of reports point to preceding viral infection, including varicella, as a potentially important risk factor for iGAS infection.[56-59] 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.[54] Over a 16-week period in 2016, 70% of a cluster of 10 iGAS cases presenting to Children's Health Ireland at Temple Street had active varicella; 60% of cases required admission to the paediatric intensive care unit.[60] Internationally reported case fatality rates range from 10% to 24% for necrotising fasciitis, and 36% to 56% for streptococcal toxic shock-like syndrome.[54, 61]

Following the COVID-19 pandemic, increases in iGAS infection among young children were reported in France, the Netherlands, Sweden and the UK.[56-58] Between

October 2022 and August 2023, the HPSC in Ireland also reported an unusual increase in notified iGAS infections, compared with previous years, particularly in children. The number of iGAS cases in Ireland in 2023 were 4.2-times higher than expected, with 533 cases notified between January and December, compared with an average of 126 cases during the pre-pandemic years of 2017-2019.[62] In the years prior to the COVID-19 pandemic, children accounted for approximately 25% of all iGAS cases but this figure increased to 41% during 2023.[62] 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.

1.3.2.3 Mortality

While death due to varicella is rare, it can and does occur. The mortality risk is highest for adults and children less than one year old. Before the introduction of universal varicella vaccination in a number of high-income developed countries, case-fatality rates for varicella were estimated at approximately 3 per 100,000 cases.[11, 13] Age-standardised annual mortality rates due to varicella over the past 10 years in England have ranged from 0.01 to 0.03 per 100,000 population.[63] Since 2012, only one notifiable 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 on CIDR was recorded as "not known".[64]

1.3.3 Treatment

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).[65] 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.[66] 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.[66, 67] Prompt intravenous antiviral therapy is recommended for individuals at high risk for severe disease and complications.[65]

1.3.4 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, typically 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, typically affecting one side of the face or body.[8] The lifetime risk of developing herpes zoster for those who have had varicella is approximately 30%[68] and rises to 50% in people aged 85 years and over.[69] Someone with herpes zoster can transmit VZV to someone who has not had varicella and is not immune, but someone with varicella cannot directly cause herpes zoster in another person.

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.[70] Herpes zoster is not a notifiable disease in Ireland. Incidence in the community is estimated from data obtained from the sentinel general practice surveillance programme for herpes zoster, but these data are likely an underestimate of true incidence.[28] 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.[29] For 2019, the most recent year that data are available, 66% of all herpes zoster notifications from sentinel general practices related to adults aged at least 50 years old.[29]

Morbidity associated with herpes zoster increases with age. 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.[71] The risk of developing post herpetic neuralgia as a result of herpes zoster has been estimated at between 5% and 30%.[72] 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.[73]

1.3.5 Economic burden

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.

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.[24] 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.[24] 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%).[24] It should be noted that data used to generate these estimates were largely imputed from varicella burden of disease data from other European countries.[24]

Studies specifically examining the economic burden of varicella in Ireland are limited. A study 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.[52]

1.4 Varicella vaccines and childhood varicella vaccination

Since Edward Jenner's seminal work on smallpox vaccination in 1796, vaccination as a public health intervention has contributed enormously to global health. In the past 50 years, vaccination has averted an estimated 154 million deaths, including 146 million among children aged less than five years.[74] With vaccines now available to prevent more than 20 life-threatening diseases, people are able to live healthier and longer lives.[75, 76] A live attenuated vaccine for varicella was first developed in Japan in the 1970s and monovalent varicella vaccines first became commercially available in the 1980s. Subsequently, the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine was approved in 2005 in the USA[77] and 2006 in Europe.[15]

Currently there are four live attenuated vaccines authorised for vaccination against varicella in Europe; the monovalent vaccines VARIVAX® (the only varicella vaccine that is marketed in Ireland and available to purchase privately)[78] and Varilrix®, and the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines, ProQuad® and Priorix-Tetra®. Both monovalent vaccines and one quadrivalent vaccine (ProQuad®) are indicated for children from 12 months of age,[79-81] while the second quadrivalent vaccine (Priorix-Tetra®) is indicated for children from 11 months of age.[82] 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. The vaccines differ in terms of recommended dosing intervals, interchangeability, and the potential for co-administration with other vaccines (**Table 1.2**).

Table 1.2 Dosage, age at vaccination and interchangeability for authorised varicella vaccines

Vaccine	Vaccine type	Age at vaccination*	Recommended dosing schedule (per Summary of Product Characteristics)	Interchangeability of varicella vaccines	Potential issues with co-administration with other vaccines
VARIVAX®[79]	Monovalent (varicella)	9-12mths	2 doses ≥3 months apart‡	Not specified in Product Summary Characteristics.	Concurrent administration of VARIVAX® and tetravalent, pentavalent or hexavalent (diphtheria, tetanus, and acellular pertussis [DTaP])-based vaccines has not been evaluated.
		12mths-12yrs	2 doses ≥1 month apart‡		
		≥13yrs	2 doses 4-8 weeks apart‡		
Varilrix®[80]	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. • A single dose of Varilrix may be administered followed by a single dose of another varicella containing vaccine.	No issues identified.
		≥12mths	2 doses ≥6 weeks (and not less than 4 weeks) apart‡		
ProQuad®[81]	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.	No issues identified.
		≥12mths	1 dose followed 1-3 months later by:‡ 2nd dose MMRV OR 1 dose monovalent		
Priorix-Tetra® [82]	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.	Separate vaccinations can 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.
		≥11mths	1 dose followed 6 weeks (and not less than 4 weeks) to 3 months later by: 2nd dose MMRV OR 1 dose monovalent		

				• 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.	

Key: MMR – measles, mumps, rubella; MMRV - measles, mumps, rubella, varicella.

*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.

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%.[13] Similar to the WHO, 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.[20]

The WHO describes the term 'routine immunisation' from two perspectives. The first relates to the foundation of the health system and immunisation system strengthening, where routine immunisation is described as the process to regularly deliver vaccines according to the national immunisation schedule.[83] The second relates to coverage improvements and refers to specific activities designed to increase routine immunisation coverage rapidly to reach stated coverage or disease control goals.[83] In the context of a particular country's routine childhood immunisation schedule, universal vaccination refers to access, where vaccination is offered to all children, is funded by the government and therefore free at the point of care for those eligible to receive it. In a number of countries, some vaccines provided under universal childhood vaccination programmes are currently compulsory under law and children must be vaccinated.[84-87] In some instances, vaccination against a specific disease may be recommended by a National Immunisation Advisory Technical Group (NITAG), but the government in that country may not have funded and implemented a vaccination programme to support that recommendation. In that case, the vaccine may be marketed in that country and available for individuals to purchase privately.

The USA was the first country to license the monovalent varicella vaccine for universal routine vaccination of persons aged at least 12 months in 1995.[88] Germany was the first country in Europe to introduce nationwide universal childhood varicella vaccination in 2004.[89] In 2018, 36 countries and regions globally recommended childhood varicella vaccination, though not all programmes were publicly funded.[90]

By 2021, this number had increased to 44 countries, 14 of which are in Europe (12 of which have publicly funded programmes).[91] However, these recommended varicella vaccination programmes are heterogeneous, with a number of important differences. These differences include the number of doses recommended, the type of vaccine administered (monovalent or quadrivalent), the age at which the first dose is recommended and the interval between doses where a two-dose schedule is recommended (**Table 1.3**).

Table 1.3 Selection of funded international childhood varicella vaccination programmes

European Countries	**Year Introduced**	**Dosage**	**Age**	**Monovalent/ Quadrivalent**	**Additional Information**
Finland[92]	2017	Two-dose	Min. 18mths - 1st dose 6yrs - 2nd dose	Mono 1st dose 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 varicella. 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[93]	2004 (1-dose) 2009 (2-dose)	Two-dose	11-14mths - 1st dose 15-23mths - 2nd dose	Mono 1st dose 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[94]	2006	Two-dose	12-15mths - 1st dose 4-6yrs - 2nd dose	Unclear	Not applicable
Hungary[85] (mandatory)	2018	Two-dose	13mths - 1st dose 16mths - 2nd dose	Mono 1st dose Mono 2nd dose	Not applicable
Iceland[95]	2020	Two-dose	12mths - 1st dose 18mths - 2nd dose	Mono 1st dose Mono 2nd dose	Not applicable
Italy[86] (mandatory)	2017	Two-dose	13-15mths - 1st dose 5-6yrs - 2nd dose	Mono/Quad 1st dose Mono/Quad 2nd dose	Not applicable
Latvia[87] (mandatory)	2008 (1-dose) 2019 (2-dose)	Two-dose	12-15mths - 1st dose 7yrs - 2nd dose	Mono 1st dose Mono 2nd dose	Not applicable
Luxembourg[96]	2010	Two-dose	12mths - 1st dose 15-23mths - 2nd dose	Quad 1st dose Quad 2nd dose	Not applicable
Spain[97]	2016	Two-dose	15mths - 1st dose 3-4yrs - 2nd dose	Mono 1st dose Mono/Quad 2nd dose	Not applicable
Other Countries	**Year Introduced**	**Dosage**	**Age**	**Monovalent/ Quadrivalent**	**Additional Information**
Australia[98]	2005 (mono) 2013 (quad)	One-dose	18mths	Quad	Two doses of monovalent vaccine are recommended for all non-immune people aged ≥14 years.
Canada[99]	2000-2007 (by province/ territory)	Two-dose	12-15mths - 1st dose ≥18mths (but no later than school entry) - 2nd dose	Mono/Quad 1st dose 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.

European Countries	Year Introduced	Dosage	Age	Monovalent/ Quadrivalent	Additional Information
New Zealand[100]	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[101]‡	1995 (1-dose) 2005 (2-dose)	Two-dose	12-15mths - 1st dose 4-6yrs - 2nd dose	Mono/Quad 1st dose Mono/Quad 2nd dose	People ≥13 years who have never had varicella or received varicella 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 varicella vaccine or have other evidence of immunity against varicella before starting school. There are eight states with a school-entry requirement of one dose of varicella vaccine or other evidence of immunity against varicella. Additional Source for European countries: ECDC Vaccination Scheduler[102]

1.5 Childhood vaccination in Ireland

Childhood vaccination has a long history in Ireland with the first vaccination against smallpox offered for all children born in Ireland in 1863. Vaccines for diphtheria and tetanus were introduced in the 1930s and the childhood immunisation schedule has continued to evolve since, with vaccines for meningococcal B and rotavirus among the more recent additions.[103] At the time this thesis was undertaken, the varicella vaccine was not included in the routine childhood immunisation schedule in Ireland. However, one of the monovalent vaccines is licensed, marketed and available to purchase privately for those who wish to pay for it. As of 2023, the immunisation schedule for children in Ireland requires five visits for vaccination up to and including 13 months of age. The schedule also includes additional vaccinations for school-aged children in junior infants (at four/five years of age), senior infants (at five/six years of age) and at 12/13 years of age. A summary of the recommended childhood immunisation schedule in Ireland is provided in **Table 1.4**.

Table 1.4 Recommended childhood immunisation schedule in Ireland 2023

Age/ School class	Vaccinations	Number of Vaccinations
2 Months	6 in 1 (DTaP/Hib/IPV/Hep B) + PCV + MenB + Rotavirus	3 injections + 1 oral
4 Months	6 in 1 (DTaP/Hib/IPV/Hep B) + MenB + Rotavirus	2 injections + 1 oral
6 Months	6 in 1 (DTaP/Hib/IPV/Hep B) + PCV + MenC	3 injections
12 Months	MMR + MenB	2 injections
13 Months	Hib/MenC + PCV	2 injections
Junior Infants (4/5 Years)	4 in 1 (DTaP/IPV*) + MMR	2 injections
Senior Infants (5/6 Years)	LAIV	1 nasal
12-13 Years	HPV + Tdap + MenACWY	3 injections

Sources: Health Service Executive. Immunisation. Primary Childhood Immunisation Schedule Available from: Immunisation Schedule - HSE.ie; Health Service Executive. Immunisation. School Programme. Available from School Programme - HSE.ie

*dTap/IPV can be given if DTaP/IPV is not available

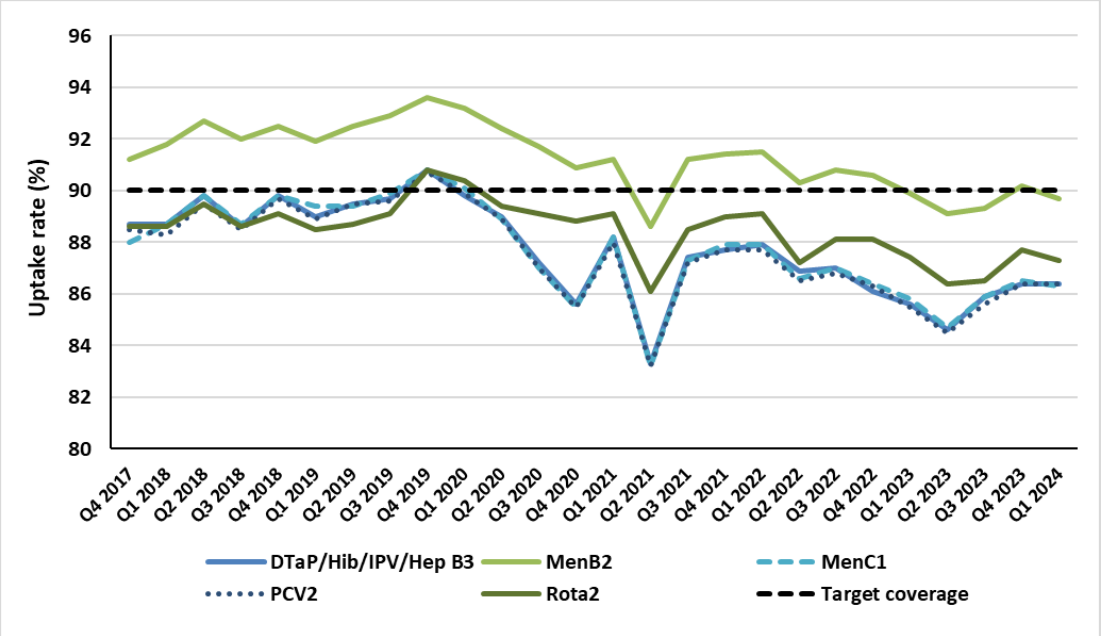
Key: DTaP - diphtheria, tetanus and acellular pertussis; HepB - hepatitis B; Hib - haemophilus influenzae b; HPV - human papilloma virus; IPV - inactivated polio virus; LAIV – live attenuated influenza vaccine; MenACWY - meningococcal ACWY; MenB - meningococcal B; MenC - meningococcal C; MMR - measles, mumps and rubella; PCV - pneumococcal conjugate vaccine; Tdap - tetanus, low-dose diphtheria and low-dose acellular pertussis.

1.5.1 Vaccine uptake

The most recent (Q1 2024) published national vaccine uptake rates at 12 months of age for the five childhood vaccines recommended up to that age, range from 86.4% for the pneumococcal vaccine to 89.7% for the meningococcal B vaccine (**Figure 1.1**).[104] In the three years preceding the COVID-19 pandemic, vaccine uptake rates at 12 months of age were consistently higher than 88% for all five vaccines,[104] but

with the exception of the meningococcal B vaccine, coverage rates were below the 90% target coverage rate set by the WHO for essential childhood vaccines.[105] Vaccines for meningococcal B and rotavirus diseases are two of the more recent additions to the childhood immunisation schedule in Ireland (2016). In Q4 2017 (the first period for which data are available) uptake rates at 12 months of age for two doses of meningococcal B vaccine and two doses of rotavirus vaccine were 91.2% and 88.6%, respectively; in Q1 2024, uptake rates were approximately one and a half percentage points lower at 89.7% and 87.3%, respectively.

Figure 1.1 National uptake rates of selected childhood vaccines in Ireland at 12 months of age over time

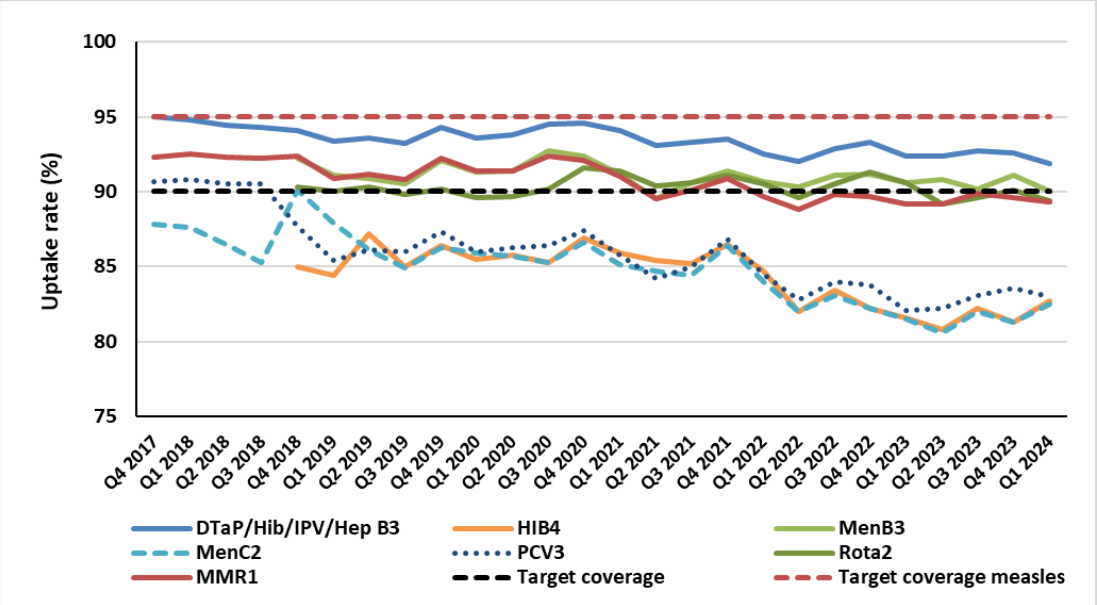


Source: Health Protection Surveillance Centre[104]
Key: DTaP - diphtheria, tetanus and acellular pertussis; HepB3 - hepatitis B 3 doses; Hib - haemophilus influenzae b; IPV - inactivated polio virus; MenB2 - meningococcal B 2 doses; MenC1 - meningococcal C 1 dose; PCV2 - pneumococcal conjugate vaccine 2 doses; Rota2 – rotavirus 2 doses.

At 24 months of age, the most recent coverage rates (Q1 2024) vary from 82.5% for two doses of the meningococcal C vaccine to 89.3% for one dose of the MMR vaccine and 91.9% for three doses of vaccine against diphtheria, tetanus, pertussis, haemophilus influenzae type b, hepatitis B and polio (**Figure 1.2**). The lowest coverage rates (between 80% and 85%) at 24 months of age are reported for four doses of vaccine against haemophilus influenzae type b (fourth dose recommended at 13 months), two doses of vaccine against meningococcal C disease (second dose

recommended at 13 months) and three doses of vaccine against pneumococcal disease (third dose recommended at 13 months). These are the recommended final dose of each of these three vaccines and they are administered at 13 months of age, one month after the previous scheduled vaccination visit. This is the shortest interval between vaccines in the childhood immunisation schedule (**Table 1.4**) and the scheduling of this visit so soon after the last may be an issue for some parents or guardians.

Figure 1.2 National uptake rates of selected childhood vaccines in Ireland at 24 months of age over time



Source: Health Protection Surveillance Centre[104]
Key: DTaP - diphtheria, tetanus and acellular pertussis; HepB3 - hepatitis B 3 doses; Hib - haemophilus influenzae b; HIB4 - haemophilus influenzae b 4 doses; IPV - inactivated polio virus; MMR1 – measles mumps rubella 1 dose; MenB3 - meningococcal B 3 doses; MenC2 - meningococcal C 2 doses; PCV3 - pneumococcal conjugate vaccine 3 doses; Rota2 – rotavirus 2 doses.

With respect to the school based immunisation programme, uptake of the 4 in 1 diphtheria, tetanus and pertussis and inactivated polio vaccines (DTap-IPV) for the academic year 2021/2022 (most recent data available) was 87%.[106] This was lower than the uptake rate of 88.3% recorded for the previous academic year. Similarly, a decline was also recorded in the uptake rate for the MMR vaccine, falling from 88% in 2020/2021 to 87.5% in 2021/2022.[106] The MMR uptake rate is currently below the rate of 95%, advised by the WHO, that is required to prevent the spread of

measles.[107] For all academic years from 2013/2014 to 2019/2020 inclusive, uptake rates for both vaccines were in excess of 90%.[106]

Uptake rates for some recommended childhood immunisations in Ireland are currently below the targets set by the WHO. This is a threat both at the individual and at the population level when considering herd immunity. Some vaccines require very high levels of uptake (for example, 95% for measles) in order to maintain effective control of a disease and thereby herd immunity, protecting those who cannot be vaccinated.[105] Vaccine hesitancy, defined at the individual level as a state of indecision and uncertainty about vaccination before a decision is made to act (or not act), is a global concern and has been identified by the WHO as one of the top 10 threats to global health.[108] Numerous surveys conducted to investigate attitudes towards COVID-19 vaccination have highlighted an escalation in the scope and scale of vaccine hesitancy in recent years.[109] Additionally, UNICEF reports that in a study of 55 countries, the public perception of the importance of vaccines for children declined during the COVID-19 pandemic in 52 countries, including in Ireland.[110] The perception of the importance of childhood vaccination in Ireland fell 6 percentage points from 91.5% to 85.5%.[110] A cross-section national survey of parental attitudes towards childhood vaccinations in Ireland, conducted between June and August 2021, reported that while there was a strongly positive sentiment towards childhood vaccinations, the most commonly identified reasons for missed vaccines were concerns about safety and vaccine side effects.[111] As such, these analyses may help to understand some of the reasons why there has been a decline in uptake rates for childhood immunisation in Ireland over the past number of years.

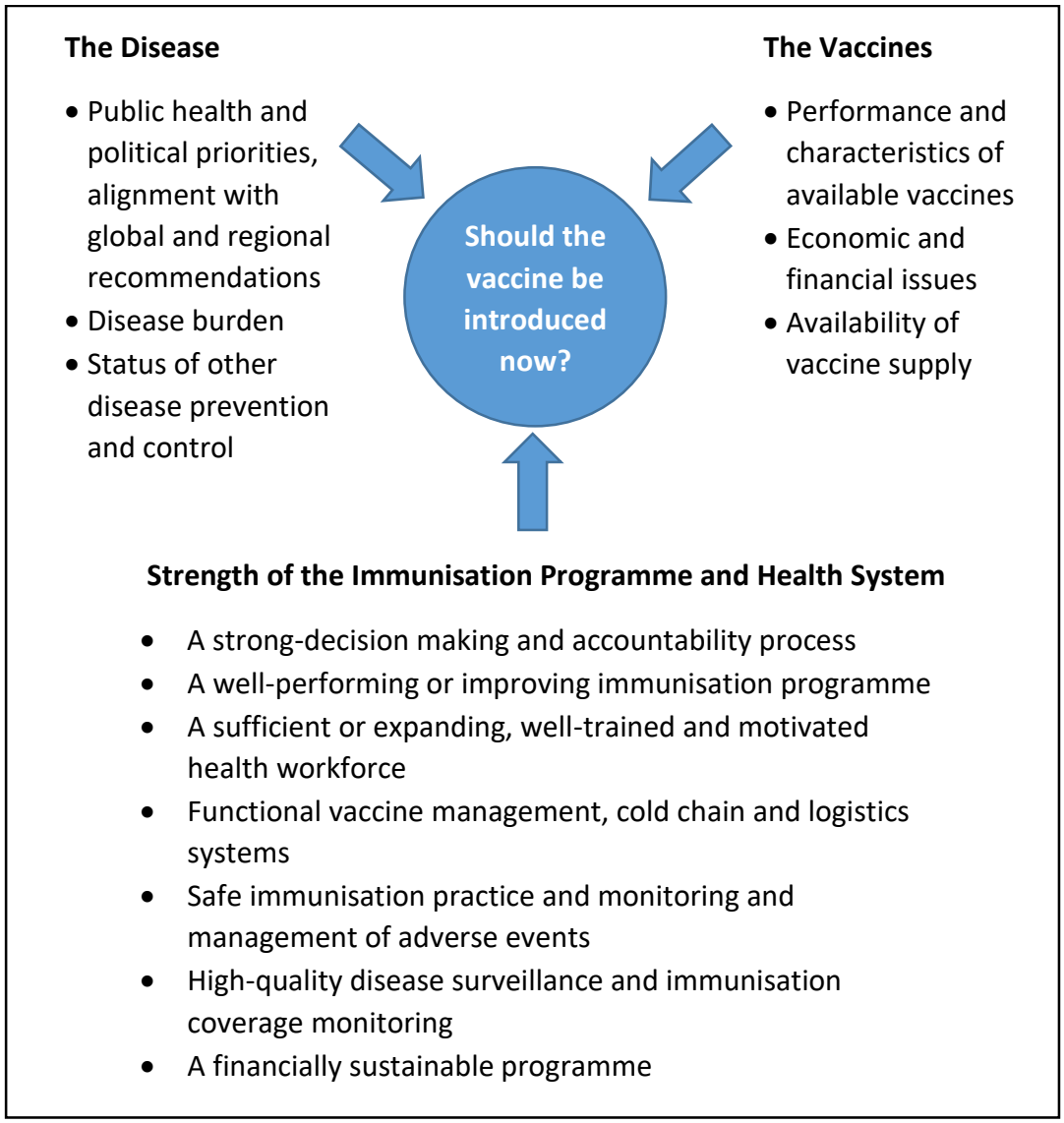
With respect to understanding varying uptake rates between different childhood vaccines that may be partly explained by concerns about the safety of specific vaccines, it is also worth considering that many vaccine-preventable diseases are unfamiliar to parents today. A number of systematic reviews have reported on the association between awareness of disease susceptibility and vaccination status, providing a plausible explanation as to why uptake rates may differ between different childhood vaccines. A 2017 systematic review, comprising 64 studies from 12 countries and covering 13 vaccines, reported strong evidence for an association

between perceived susceptibility to an illness and vaccination, with perceived low susceptibility to the illness self-reported as a reason against vaccination.[112] Similarly, a 2022 systematic review, comprising 34 studies across all WHO regions, reported that awareness of disease susceptibility was an important determinant of vaccination status, with low perceived disease susceptibility often cited as a barrier to vaccine uptake.[113]

1.6 Evidence-based decision making

The WHO identifies a number of considerations, that can be grouped under three key areas, when making policy decisions on the addition of a new vaccine to a national immunisation programme **Figure 1.3**.[114] The first area concerns the disease that the vaccine targets and specifically the magnitude of the disease burden and whether the disease is a public health priority. The second relates to the vaccine, including its safety and effectiveness as well as the cost, affordability and cost effectiveness. The third area concerns capacity of the existing immunisation programme to support an additional vaccine and the ability of the health system to implement and sustain the proposed changes to the existing programme. Several analytic tools have been identified to support evidence-based decision making in public health which can be used to assess some of these key considerations identified by the WHO. The tools include systematic review and economic evaluation,[3, 115-118] where systematic review is a means to identify specific policy that is likely to be effective and safe and economic evaluation is a means to document the potential impact of that policy.[119]

Figure 1.3 Key issues to consider when deciding on the introduction of a new vaccine to a national immunisation programme



Source: WHO 2014[114]

1.6.1 Systematic review as a methodology

By the 1990s, the volume of published scientific literature to guide clinical practice had increased significantly but the quality of reviews of primary research were generally considered subjective and scientifically unsound.[120-123] As a result, it became increasingly difficult for medical practitioners to obtain reliable evidence to support informed health-care decision-making, with calls for more robust methods for literature searching, quality assessment of primary research studies and synthesis of results.[121, 124] In response to these calls, the Cochrane Collaboration, founded in 1993, was established with an aim of informing clinical practice by conducting,

disseminating and maintaining systematic reviews of medical interventions. A systematic review has since been defined as an objective and standardised review of the evidence on a clearly formulated research question, using systematic and explicit methods to identify, extract, appraise and synthesize the evidence.[125, 126] The types of reviews defined and produced within the Cochrane Database of Systematic Reviews also includes overviews of reviews and rapid reviews. Overviews of reviews are described as reviews which synthesize information from multiple systematic reviews on related research questions and rapid reviews are described as systematic reviews accelerated through streamlining or omitting specific methods.[125]

1.6.2 Economic evaluation

The ever-increasing demand for and rising cost of providing healthcare means that choices have to be made between competing health technologies. Decisions have to be made as to which health technologies will be funded and offered to citizens through publicly funded health systems. Therefore, economic considerations have gained an increasingly important role in organising, managing and assessing health systems.[127, 128] At a micro level, economic considerations include assessments of value for money, or economic evaluation, of individual health technologies. Economic evaluation has thus become a frequently used tool to support decision making regarding the allocation of healthcare resources and the adoption of new technologies. It answers the question as to whether the expected benefits of an intervention are worth the resources expended.

Economic evaluation provides a framework for the organised consideration of the effects of health interventions on health, healthcare costs and other relevant effects.[129] It involves the identification, measurement, valuation and comparison of the costs and consequences of alternative courses of action, addressing the issue of choice between competing alternatives.[129] It encompasses a number of techniques that are differentiated based on how the consequences of an intervention, rather than the costs, are measured and valued (**Table 1.5**). In Ireland, cost-utility analysis (CUA) is the preferred type of economic evaluation used to inform healthcare policy

decision-making and the quality-adjusted life year (QALY) is the preferred outcome measure.[130]

Table 1.5 Types of economic evaluation

Type of study	Cost measure	Outcome measure	Measure of efficiency
Cost-minimisation analysis	Monetary units	None – assumed to be equivalent	Cost
Cost-consequence analysis	Monetary units	Disaggregated range of outcomes (e.g. primary clinical outcome and quality of life and patient satisfaction)	Disaggregated range of costs and outcomes
Cost-benefit analysis	Monetary units	Monetary units	Net present value
Cost-effectiveness analysis	Monetary units	Natural units (e.g. life years gained, points of blood pressure reduction)	Cost per additional unit effect
Cost-utility analysis (sub-type of cost-effectiveness analysis)	Monetary units	Healthy years (e.g., quality-adjusted life years gained)	Cost per quality-adjusted life year gained

Sources: Drummond et al. 2015;[129] HIQA 2020;[130] Brazier et al. 2017.[131] WHO 2019[132]

1.6.3 Decision analytical modelling

Increasingly, evidence to support decisions regarding healthcare policy originates from multiple sources rather than a single trial and therefore data need to be integrated in a systematic manner to aid decision making.[133] When such circumstances arise and when considering value for money specifically, decision analytical modelling (DAM) provides a framework for economic evaluation.[134] In DAM for economic evaluation, mathematical relationships are used to construct the decision problem or the question(s) relating to resource allocation, and the model incorporates the possible consequences from a set of alternative options being evaluated.[135] By including the likelihood, costs and outcomes of each consequence, DAM enables the calculation of the expected cost and outcome of each option under consideration and therefore a comparison of the possible alternatives.

1.6.3.1 Types of decision analytical models

There are many different types of models applied in DAM, including decision trees, state transition models such as Markov (cohort) models, patient level simulation models, dynamic transmission models, and discrete event simulation models. The choice of model will be dependent on a range of factors including model appropriateness for the decision problem, time horizon of the decision problem, independence between individuals, ease and speed of model development and the requirements of the decision maker.[134, 136, 137] **Table 1.6** provides a summary of the main types of decision model structures and decision problem model suitability.

Table 1.6 Summary of types of decision analytical models

Model type	General description	Type of decision problem that model is best suited for
Decision tree	Diagram of the risk of events and health states over a fixed time horizon.	Interventions for which the relevant time horizon is short and fixed.
Markov (cohort) model	Simulates a hypothetical cohort of individuals through a set of health states over time.	Modelling interventions for diseases or conditions that involve risk over a long time horizon and/or recurrent events.
Microsimulation (individual) model	Simulates one individual at a time; tracks the past health states of an individual and models the risk of future events stochastically.	Modelling complex disease processes, when Markov models are too limiting.
Dynamic transmission model	System of differential equations that simulates the interactions between individuals and the spread of disease.	Modelling interventions for communicable diseases, such as vaccination.
Discrete event simulation model	Simulates one individual at a time as well as interactions among individuals or within a health care system.	Evaluating alternative health care systems (e.g., workflow, staffing) though offers flexibility to address questions in several different areas.

Source: Kuntz et al. 2013[138]

The decision tree is the simplest and most widely used decision model for economic evaluation. Where the possible decisions are relatively straightforward and involve a fixed sequence of events that are not time dependent, a decision tree is usually appropriate.[139, 140] However, where the prognosis is complex and or long-term, the decision tree can quickly become unwieldy and time-consuming to develop and

analyse.[129] For example, patients often respond differently to treatment for a disease with some responding sooner than others, some progressing to recovery sooner and some relapsing after recovery. Where these processes can't be modelled using a decision tree, a Markov model is a commonly used approach. It provides a way in which to structure and analyse the evolution of health states and the dynamic processes associated with a particular disease.[139] Although the Markov model provides greater flexibility than decision trees, it also has some limitations. The main limitation is that of the Markov assumption, where it is assumed that once an individual moves from one state to another, the model has 'no memory' regarding the health state from which an individual has come. The main implication of this is that it may not be possible to model a process where future events depend on past events without adding additional states and increasing the likelihood of the model becoming unwieldy.[129, 135]

The challenges associated with incorporating time dependency and memory into decision analytic models can be overcome by adopting individual patient-level microsimulation models. These models track the progression of individuals, rather than a cohort, through health states and dynamic processes associated with a particular disease. While they offer greater structural flexibility than the Markov cohort model, enabling the history of individuals to be captured and incorporated in the analysis, they do present difficulties. Additional evidence and a greater number of parameters are typically required to populate individual patient-level microsimulation models and the computational burden associated with the uncertainty analysis can be time consuming.[129, 135]

A key assumption in decision tree, Markov and individual microsimulation models is that the individuals being modelled are independent of each other with respect to their health and interaction between individuals is not considered to be of importance. In the case of communicable infectious diseases, the risk of an individual contracting the disease is dependent on the force of infection which in turn is partly dependent on the number of infectious individuals in the population at a given time and contact with these individuals. The communicable nature of an infectious disease thus impacts the effectiveness of an intervention and decision analytic models

developed to assess the cost effectiveness of interventions may need to account for these features. Unlike the previous three models discussed above, a key feature of dynamic transmission models is their ability to capture the interaction of individuals and allow for a changing force of infection over time.[129, 135] In comparison to decision tree and Markov models, dynamic transmission models are analytically more complex and require more computing power to implement.

Lastly, discrete event simulation models are similar to individual microsimulation models in that they simulate individual patient trajectories. However, rather than considering specific health states that individuals can be in, discrete event simulation models structure the problem around events or clinically relevant occurrences that can be of any duration, allowing for more structural flexibility. Higher levels of complexity and interactions between individuals and between individuals and the environment can also be accommodated with discrete event simulation models.[141] Similar to individual microsimulation models, the data requirements and computational burden associated with discrete event simulation models are greater than those for decision tree and Markov models.

1.7 Health Technology Assessment in Ireland

In Ireland, the use of health technology assessment (HTA) is increasingly being used to inform national health policy decisions.[142] HTA was first conceptualised in the USA almost 50 years ago and the field has evolved and grown considerably since then.[143] In the early years of HTA in the USA, 'efficacy' was emphasised given the objective of health care was to improve health. The increasing expenditure on health care was also an important motivation for the development of HTA and so HTA involved synthesising available evidence mainly relating to the efficacy and cost effectiveness of health interventions and presenting it in a helpful manner to health policy makers.[143] HTA has recently been defined as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle and is used to inform decision-making in order to promote an equitable, efficient, and high-quality health system.[144, 145] HTA is a method of evidence synthesis that considers evidence regarding clinical effectiveness, safety,

cost-effectiveness, social, ethical, and legal aspects of the use of a health technology.[146] Under the Health Information and Quality Authority's (HIQA) statutory remit to evaluate the clinical and cost effectiveness of health technologies in Ireland,[147] the Department of Health requested HIQA to conduct a HTA of the expansion of the childhood immunisation schedule in Ireland to include varicella vaccination. In my professional role with HIQA, I was responsible for leading this HTA and therefore, the research outputs of this thesis (sections 1.1 to 1.5 inclusive of chapter 1, and chapters 2, 3, 4 and 5) are also contained within the HTA that was published in July 2023.[148]

1.8 Thesis structure and outline

The order and subject of the chapters of this thesis that follow are described below and the thesis research chapters are summarised in **Table 1.7**:

- **Chapter 2** is a literature review, comprising a published overview of systematic reviews of the clinical effectiveness of alternative childhood varicella vaccination strategies.
- **Chapter 3** is a literature review, comprising a published overview of systematic reviews of the safety of varicella vaccination strategies.
- **Chapter 4** is a literature review, comprising a rapid review of the methodology for the economic modelling of childhood varicella vaccination.
- **Chapter 5** is an economic evaluation comprising a published cost-utility analysis of universal childhood varicella vaccination in Ireland.
- **Chapter 6** comprises a discussion of the main findings including overall interpretation, implications of the findings for public health policy and practice, strengths and limitations of the thesis, and overall conclusions.

Table 1.7 Summary of thesis research chapters

Chapter	Research question	Methodology	Dissemination/ Publication Status
2	What is the clinical efficacy and effectiveness of alternative vaccination strategies for active immunisation against varicella in immunocompetent children?[†]	Overview of systematic reviews	Published

Chapter	Research question	Methodology	Dissemination/ Publication Status
3	What is the safety profile of alternative vaccination strategies for active immunisation against varicella in immunocompetent children?[†]	Overview of systematic reviews	Published
4	What approaches have been used to model the expected costs and benefits of childhood varicella vaccination?	Rapid review	Commentary piece on the developments in methodology to be submitted for publication[‡]
5	Is universal childhood varicella vaccination cost effective in Ireland?	Cost-utility analysis	Published

[†]Research questions two and three are limited to immunocompetent children as live attenuated vaccines (such as the varicella vaccine) should not be routinely given to those who are clinically immunosuppressed as it could lead to serious infection.

[‡]A protocol for a systematic review of the cost effectiveness of varicella vaccination programmes was identified on PROSPERO during the scoping stage of this review.[(149)] The authors were contacted and they confirmed that the systematic review was ongoing. As the systematic review was subsequently published in 2023,[(150)] and is very similar to the rapid review conducted as part of this thesis, the rapid review has not been submitted for publication.

2 Clinical efficacy and effectiveness of alternative varicella vaccination strategies: An overview of reviews

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2.1 Abstract

A number of countries have implemented universal childhood varicella vaccination programmes over the past 30 years. However, strategies differ in terms of dosing schedule (one- or two-dose), type of vaccine(s) recommended (monovalent, quadrivalent measles-mumps-rubella-varicella, or both), age at vaccination, and dosing interval for a two-dose schedule. An overview of reviews was undertaken to assess the existing systematic review evidence of the clinical efficacy/effectiveness of alternative varicella vaccination strategies. A comprehensive search of databases, registries and grey literature was conducted up to 2nd February 2022. Two reviewers independently screened, extracted data and assessed the methodological quality of included reviews. A total of 20 reviews were included in the overview; 17 assessed the efficacy/effectiveness of one-dose strategies and 10 assessed the efficacy/effectiveness of two-dose strategies. Although the quality of most reviews was deemed 'critically low', there was 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 reviews, the evidence suggests that two-dose strategies are more efficacious/effective than one-dose strategies in preventing varicella of any severity, but that both strategies have similar high efficacy/effectiveness in preventing moderate or severe varicella. Based on this evidence in this overview of reviews, a key consideration for policymakers on the possible introduction of a childhood varicella vaccination programme and the choice between a one- or two-dose strategy, will be whether the objective of a programme is to prevent varicella of any severity or to prevent moderate to severe varicella.

2.2 Introduction

Varicella-zoster virus (VZV) is a member of the herpesvirus family and is associated with two distinct clinical syndromes, varicella, resulting from primary infection, and herpes zoster, resulting from reactivation of the virus. Varicella is a frequently occurring, vaccine-preventable, acute infectious disease, mainly affecting children. Without vaccination the annual incidence in EU/EEA countries typically approximates the annual birth cohort.[20] Approximately 96% of those who are exposed to the VZV and who are not immune due to a history of varicella or vaccination, will develop the disease.[8] Varicella is characterised by a pruritic rash that typically 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.[39] The disease is usually mild, although complications can occur and may include skin and soft tissue superinfections, as well as neurological, respiratory system, gastrointestinal, hepatic and haematological complications requiring hospitalisation.[11, 151] The burden of VZV infection globally is significant. The World Health Organization (WHO) has estimated that VZV is responsible for approximately 4.2 million severe complications leading to hospitalisation and 4200 related deaths globally each year.[13] Additionally, the societal burden associated with varicella is considerable due to both school and work absenteeism for patients and productivity loss for their caregivers.[11]

A live attenuated vaccine for varicella was first developed in Japan in the 1970s and varicella vaccines first became commercially available in the 1980s. The USA was the first country to license the monovalent varicella vaccine for universal routine vaccination of persons aged at least 12 months in 1995.[88] Germany was the first country in Europe to recommend nationwide universal childhood varicella vaccination in 2004.[89] Approval for the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine followed in 2005 in the USA[77] and in 2006 in Europe.[15]

The WHO has advised 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 ≥80%.[13] In 2018, it was reported that 36 countries and regions globally had

introduced universal varicella vaccination (UVV).[90] However, these established varicella vaccination programmes are heterogeneous.[14, 152] Varying strategies have been implemented with a number of important differences between them, including the dosing schedule (one-dose or two-dose), the type of varicella vaccine(s) recommended (monovalent, quadrivalent MMRV or both), the age at which the first dose is recommended and the interval between vaccines where a two-dose schedule is in place.

A number of systematic reviews assessing the efficacy and or effectiveness of varicella vaccines have been published over the last 40 years. Early reviews are 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.

The aim of this overview of reviews was to produce a comprehensive assessment of the current evidence of the clinical efficacy and effectiveness of alternative varicella vaccination strategies. The overview should also help to inform policy decisions where the introduction of UVV is being considered and an assessment of alternative strategies is being undertaken, or where existing UVV programmes are under review.

2.3 Methods

An overview of reviews was conducted in accordance with a pre-defined protocol that was registered on PROSPERO (registration number CRD42022312325).

2.3.1 Search strategy and selection of systematic reviews

A single search was conducted to retrieve systematic reviews on the efficacy, effectiveness and safety of alternative varicella vaccination strategies, with the latter outcome reported in a separate paper.[153] A comprehensive electronic search was

performed in Embase (Elsevier), Medline (EBSCO), the Cochrane Library and Google Scholar on 2nd February 2022, with databases searched since inception (ranging from 1966 for Medline (EBSCO) to 2004 for Google Scholar. The SYSVAC and PROSPERO registries were also searched to identify relevant reviews and registered protocols for forthcoming systematic reviews. These searches were supplemented by an extensive grey literature search (**Appendix A 2.1**). All search strings, developed in consultation with an information specialist, dates of searches and search results are provided in the supplementary file (**Appendix A 2.1**). 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.

2.3.2 Data extraction and management

Titles and abstracts of potentially eligible reviews were screened independently by two reviewers using Covidence software.[154] Full text reviews were independently assessed for eligibility by two reviewers according to the pre-specified inclusion and exclusion criteria outlined in **Table 2.1**. Data extraction 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.

2.3.3 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".[155] Disagreements were resolved by discussion and with third party arbitration, when required.

Table 2.1 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 • alternative dosing schedule • alternative dosing interval • alternative age at vaccination • co-administration with another vaccine
Outcomes	**Efficacy/effectiveness** • mortality associated with varicella • hospitalisation associated with varicella • severe varicella • incidence of varicella • incidence of breakthrough varicella • long-term persistence of protection based on incidence of breakthrough varicella over time • incremental vaccine effectiveness (e.g., for 2-dose versus 1-dose or for long versus short interval between doses)
Study design	**Include:** • reviews with the following key characteristics: o a clearly stated set of objectives with an explicit, reproducible methodology o a systematic search of at least two databases that attempts to identify all studies that would meet the eligibility criteria o a systematic presentation, and synthesis, of the characteristics and findings of the included studies. o reviews reporting on at least one outcome of interest **Exclude:** • reviews only reporting data on immunocompromised children • reviews only reporting data on persons ≥ seven years of age at vaccination • reviews that incorporate theoretical studies or text and opinion as their primary source of evidence • reviews that are published as an abstract only • eligible reviews that have been updated and the updated review is included

2.3.4 Data synthesis

Summary characteristics of included reviews and overall findings are presented in table format by dosing schedule. 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 MMRV (where the vaccine type was not specifically reported). Summary output figures were developed where appropriate.

2.3.5 Overlap of included reviews

Overlaps of original research studies in each of the included reviews were identified where possible. The overall 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.[156] A CCA of 0-5 indicates slight overlap, 6-10 moderate overlap, 11-15 high overlap and >15 very high overlap.[156]

2.3.6 Reporting

The reporting of this overview of reviews adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.[157]

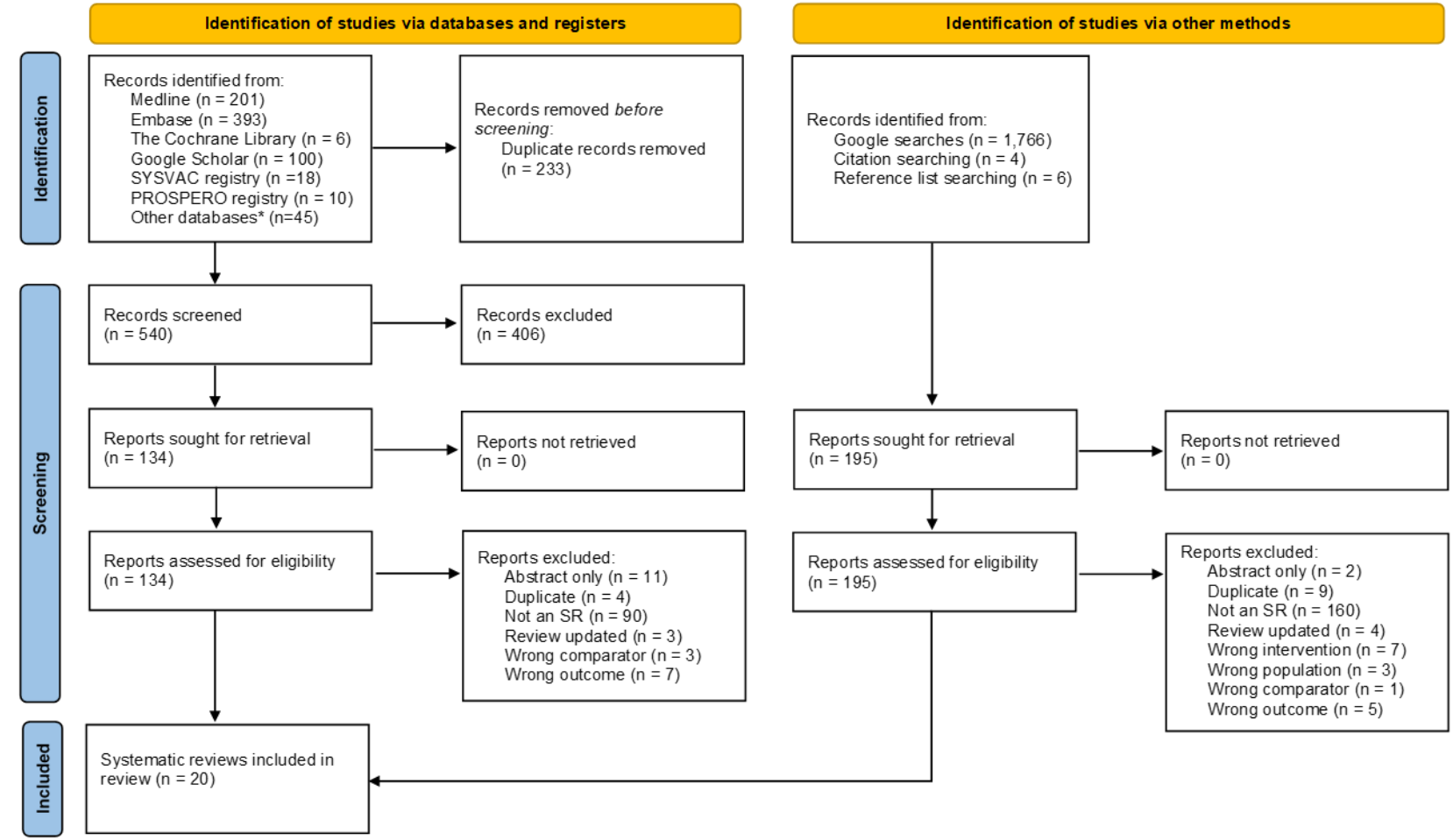
2.4 Results

2.4.1 Search findings

After removing duplicates, the initial search (for efficacy, effectiveness and safety studies) 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 (efficacy, effectiveness and safety) 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 (**Appendix A 2.2**), 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 ten reviews were identified from reference checking and forward citation searching of included reviews, three of

which were deemed eligible for inclusion, giving a final total of 20 eligible systematic reviews (**Figure 2.1**).

Figure 2.1 PRISMA 2020 flow diagram of included studies



*TRIP database and International Health Technology Assessment database

Key: SR – systematic review

2.4.2 Characteristics of included reviews

In total, 20 systematic reviews were identified that met the inclusion criteria for this review of the efficacy and effectiveness of varicella vaccination. The most recent specified end search date within these reviews was September 2019.[158] Of the 20 reviews, five reviews included randomised controlled trials (RCTs) and observational studies[159-163] (including one[163] that also included four previously published systematic reviews); 13 reviews included observational studies only;[88, 158, 164-174] one review included four previously published systematic reviews and observational studies;[175] and the final review included two previously published systematic reviews.[176] Of the eight systematic reviews that were themselves included in eligible systematic reviews for this overview, only three met our pre-defined eligibility criteria (**Table 2.1**) for a systematic review and were therefore included in this overview.[162, 164, 165]

Ten of the 20 reviews that assessed efficacy/effectiveness provided a meta-analysis. Of these, five had no geographic limitation,[159-161, 164, 165] three included RCTs[159-161] and five were based on primary observational studies from China only.[158, 166-169] The remaining ten reviews provided a narrative summary of findings. Of these, five had no geographic limitation,[162, 163, 174-176] three included RCTs[162, 163, 175] and five provided a synthesis of the experience with varicella vaccination specifically in Italy and Germany,[88] Central and Eastern Europe,[173] the Middle East,[170] Latin America and the Caribbean,[171] and the Asia-Pacific region.[172] Completed data extraction tables for all included reviews are provided in the supplementary file (**Appendix A 2.3**).

2.4.3 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, by outcome

and by 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 (VE) against 'varicella of any severity' and 'all varicella'; for the purpose of this review, these terms have been considered to be synonymous with the term 'varicella of any severity' used for consistency.

2.4.3.1 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[159, 161, 164-169] and nine reviews providing a narrative synthesis of findings.[88, 162, 170-176] A summary of the characteristics of reviews that included a one-dose strategy is provided in **Table 2.2**, with a narrative summary of results by outcome and vaccine type provided below.

Table 2.2 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(s)	Type of synthesis	Authors overall conclusion	Risk of bias conducted	Overall quality of evidence conducted	AMSTAR 2 Rating for SR
Al Kaabi 2020[170]	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[171]	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	<u>Costa Rica and Uruguay:</u> 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[164]‡	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

Author and Year	Population	Vaccine type (brand)	Concurrent administration with another vaccine	Duration of follow-up	Main outcome measure(s)	Type of synthesis	Authors overall conclusion	Risk of bias conducted	Overall quality of evidence conducted	AMSTAR 2 Rating for SR
Benchimol 2021[176]	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[159]	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[175]	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 possibility of	×	✓	Critically Low

Author and Year	Population	Vaccine type (brand)	Concurrent administration with another vaccine	Duration of follow-up	Main outcome measure(s)	Type of synthesis	Authors overall conclusion	Risk of bias conducted	Overall quality of evidence conducted	AMSTAR 2 Rating for SR
							two doses may be considered.			
Goh 2019[172]	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[166]‡	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[88]	Persons who received varicella vaccination as part of a paediatric varicella vaccination program in Italy and Germany.	Monovalent in Italy NR for Germany	NR	Italy: up to 4yrs after introduction of UVV Germany: various including up to 10yrs post vaccination	<u>Italy:</u> Incidence of varicella; Hospitalisation and complications associated with varicella <u>Germany:</u> 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. Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively.	✓	×	Low

Author and Year	Population	Vaccine type (brand)	Concurrent administration with another vaccine	Duration of follow-up	Main outcome measure(s)	Type of synthesis	Authors overall conclusion	Risk of bias conducted	Overall quality of evidence conducted	AMSTAR 2 Rating for SR
Marin 2016[165]	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. The second dose adds improved protection against all varicella.	×	×	Critically Low
Meszner 2019[173]	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[174]	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[162]	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

Author and Year	Population	Vaccine type (brand)	Concurrent administration with another vaccine	Duration of follow-up	Main outcome measure(s)	Type of synthesis	Authors overall conclusion	Risk of bias conducted	Overall quality of evidence conducted	AMSTAR 2 Rating for SR
Xu 2019[169]‡	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[167]	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[161]	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[161]	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

Outcome: Efficacy and effectiveness in preventing varicella (any severity)

Monovalent vaccine

The pooled efficacy of one-dose 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%, ^{I2}=0%; 3 RCTs, n=approx. 3,000; high-certainty evidence [GRADE] reported in review).[159] Two pooled estimates (from observational studies) reported VE in excess of 80% against varicella of any severity; VE = 81% (95% CI: 78 to 84%, I^2 = 88%; 42 observational studies), with a median time of less than 10 years since vaccination)[165] and VE= 86% (95% CI: 78 to 92%, I^2=0%; 2 case-control studies), when administered with MMR.[159] An analysis of the sources of heterogeneity was not conducted in the former review.

Quadrivalent MMRV vaccine

The effectiveness of one-dose quadrivalent MMRV vaccine was reported in two reviews.[159, 165] Compared with no vaccination, the pooled VE of one-dose quadrivalent MMRV against varicella of any severity, was 75% (95% CI: 41 to 89%, I^2=98%; 4 cohort studies).[159] The review reported that studies included in the meta-analysis did not provide sufficient detail to enable an analysis of the sources of heterogeneity. In a second review, VE was reported at 55% (95% CI: 8 to 78%; 1 cohort study) against varicella of any severity.[165]

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.[162] Using the Canadian Task Force on Preventive Health Care methodology, the review

reported this as Level I evidence.[162] 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.

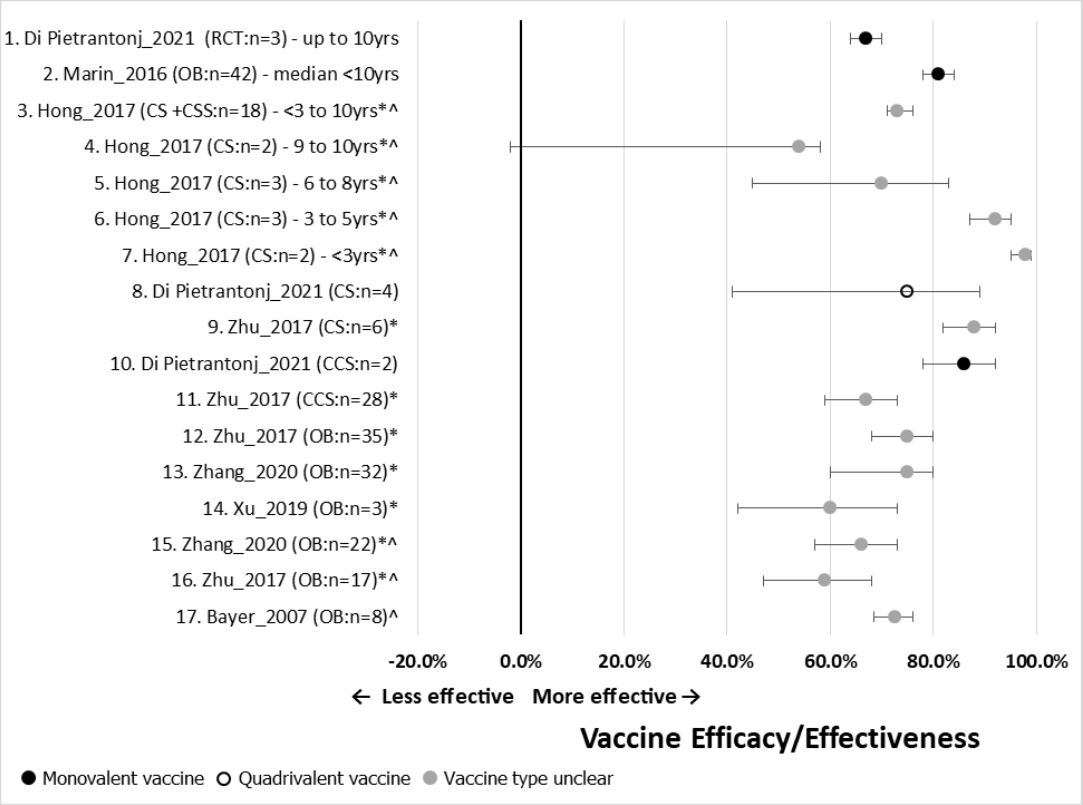
Five reviews conducted a meta-analysis of one-dose VE in preventing varicella, compared with no vaccination, without specifying the type of vaccine.[164, 166-169] Of the five reviews, four included primary studies from China only.[166-169] All five reviews reported VE in outbreak settings, either exclusively (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.[167, 168] In a third review, pooled estimates by time since vaccination were provided.[166] Overall, pooled estimates of one-dose VE 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,[166] 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.[166]

An additional five reviews provided a narrative synthesis of one-dose VE 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.[88] Similarly, the review covering Latin America and the Caribbean reported VE (from a single case-control study in regions of Brazil), against varicella of any severity, of 86% in children aged 15-35 months.[171] Three further reviews reported VE between 80 and 85% for one-dose vaccination against varicella of any severity.[162, 174, 175] The population specified in one review was children less than five years old,[162] and strength of evidence was deemed Level 1 and Level 2 evidence [SORT scale] in a second review.[175] In outbreaks in primary schools, overall VE for the prevention of varicella was reported at 72.5% (based on a meta-analysis of 14 studies), but varied considerably (20 to 100%) between studies.[175]

Figure 2.2 provides an overall summary of the 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 2.2 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.

Outcome: 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.[159] In the only review that conducted a meta-analysis, pooled VE (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).[165] Possible sources of heterogeneity were not investigated in this review. A single narrative review reported similarly high VE of 95 to 100% for the prevention of moderate to severe disease (Level 1 and Level 2 evidence [SORT scale] reported from two included systematic reviews).[175]

Quadrivalent MMRV vaccine

In a single review, VE for one-dose quadrivalent MMRV against severe varicella, was reported at 100% (1 cohort study).[165]

Monovalent or quadrivalent MMRV vaccine (vaccine type unclear)

One-dose VE against moderate or severe disease was reported in two reviews where the vaccine type was not specified.[174, 175] VE of between 95 and 100% against moderate and severe varicella combined was reported in both reviews (Level 1 evidence [SORT scale] in one systematic review)[175], while VE of 100% against severe varicella was reported in one review (17 studies in total).[174]

Outcome: Incidence of breakthrough varicella

Monovalent and quadrivalent MMRV vaccine (vaccine type unclear)

A single review assessed the incidence of breakthrough varicella (BV) after one- dose varicella vaccination.[161] 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).[161] 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.[161] Sources of heterogeneity, identified in a meta-regression, included study design and vaccine type.

Other outcomes

A number of reviews reported the impact of one-dose UVV from surveillance studies that examined incidence of varicella, ambulatory visits, complications, hospitalisation and morbidity associated with varicella. In summary, varying reductions in incidence of varicella was reported across a number of countries and regions (Brazil,[171] Costa Rica,[171] Germany,[88, 174] Italy,[88] Taiwan[172] and Uruguay[171]) following the introduction of one-dose UVV. Australia and South Korea were exceptions where the apparent increase in incidence of varicella is perhaps explained by historical under reporting of cases and the impact of introducing mandatory notification of varicella cases.[172] Similarly, varying reductions in hospitalisations and or complications associated with varicella were reported in Australia,[172] Costa Rica,[171] Germany,[88] Italy,[88] Turkey[170] and Uruguay following the introduction of one-dose UVV.[171] These findings are summarised in **Table 2.3**.

Table 2.3 Findings from systematic reviews reporting the impact of one-dose universal varicella vaccination

Outcome	Vaccine type	Review	Country/ Region	Finding
Incidence of varicella	Monovalent	Kaufmann 2020[88]	Italy	In a number of pilot regions in Italy, where regional implementation of one-dose UVV began in 2003, surveillance studies reported that incidence of varicella decreased by 30-80% depending on coverage rates.
		Arlant 2019[171]	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).
		Arlant 2019[171]	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.
	Monovalent/ quadrivalent	Kaufmann 2020[88]	Germany	Surveillance studies have reported decreased incidence of 63 to 75% in children less than four years old following one-dose UVV introduction.
		New Zealand National Health Committee 2012[174]	Germany	Evidence from a sentinel dataset from Germany demonstrated 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.
		AlKaabi 2020[170]	Turkey	Comparing those vaccinated to those not vaccinated, the incidence of varicella was lower in vaccinated children aged two to 15.5 years old. However, risk of varicella was 3.5 times higher in children vaccinated at least five years previously compared to those vaccinated more recently.
		Arlant 2019[171]	Florianapolis and Sao Paulo, Brazil	Reductions in incidence of varicella were reported in the Florianapolis and Sao Paulo areas of Brazil after the introduction of one-dose vaccination.
		Goh 2019[172]	Taiwan	A 2.9 to 3.8 fold reduction in incidence of varicella was reported (3 studies) in Taiwan when the pre- and post-UVV eras were compared.
		Goh 2019[172]	Australia	An increase in incidence was reported when the pre- and post-UVV eras were compared. Against a backdrop of a coverage rate of 78.4% reported two years after the introduction of UVV, the authors reported that the apparent low number of total cases highlights that there are possibly issues with under reporting, impacting on the reliability of the data.

Outcome	Vaccine type	Review	Country/ Region	Finding
		Goh 2019[172]	South Korea	An increase in incidence was reported when the pre- and post-UVV eras were compared. However, 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 reflects 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.
Varicella-related hospitalisation and complications	Monovalent	Kaufmann 2020[88]	Regions of 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 one-dose UVV. 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) was also reported.
		Arlant 2019[171]	Costa Rica	Hospitalisations associated with varicella and hospitalisations for complicated varicella fell by 86% and 98% respectively 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.
		Arlant 2019[171]	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.
	Monovalent/ quadrivalent	Kaufmann 2020[88]	Germany	Over a six year period following the introduction of one-dose UVV in Germany, hospitalisations associated with varicella decreased by 65%. 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.
		Goh 2019[172]	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).
		AlKaabi 2020[170]	Turkey	The incidence of complications with varicella in non-hospitalised children in an outbreak was lower in vaccinated children compared with non vaccinated children; incidence of hospitalisation with varicella for children aged one to five years was also lower in the vaccinated cohort.

Outcome	Vaccine type	Review	Country/ Region	Finding
Mortality	Monovalent/ quadrivalent	Goh 2019[172]	Taiwan	A single study 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.
		Arlant 2019[171]	Costa Rica	No difference in mortality associated with varicella was reported after UVV introduction.
		Pallas Health Research and Consultancy 2011[163]	USA	During the 12 years of the mostly one-dose programme in the USA, the average age-adjusted mortality due to varicella as an underlying cause of death decreased 88% to 0.05 per 1 million population during the period 2005–2007, with a reduction of 97% among persons aged less than 20 years.

2.4.3.2 Two-dose varicella vaccination

Ten reviews assessed the efficacy/effectiveness and or the impact of a two-dose varicella vaccination schedule, with four reviews providing a meta-analysis[158, 159, 165, 169] and six reviews providing a narrative synthesis of findings.[88, 170, 171, 174-176] A summary of the characteristics of reviews that included a two-dose strategy is provided in **Table 2.4**, with a narrative summary of results by outcome and vaccine type provided below.

Outcome: Efficacy/effectiveness in preventing varicella (any severity)

Monovalent vaccine

Two reviews conducted a meta-analysis and reported similar pooled estimates of VE of two-dose monovalent varicella vaccination against varicella of any severity, compared with no vaccination; VE = 92% (95% CI: 88 to 95%, I^2 = 57%; 4 cohort and 4 case-control studies)[165] and VE = 95% (95% CI: 86 to 99%, I^2=0%; 2 case-control studies) when administered with MMR.[159] Possible sources of heterogeneity were not investigated in the former review.

Quadrivalent MMRV vaccine

The efficacy of two-dose quadrivalent MMRV 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] reported in review).[159] Two reviews reported VE of two-dose quadrivalent vaccination against varicella of any severity, compared with no vaccination; pooled VE of 87% (95% CI: 86 to 87%, I^2=0%; 2 cohort studies) and VE 91% (95% CI: 65 to 98%; one cohort study).[165]

Monovalent or quadrivalent MMRV vaccine (vaccine type unclear)

A meta-analysis of studies from China only reported a pooled VE 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] reported in review).[158] In sub-group analysis, the estimate was lower in outbreak settings (VE = 87%, 95% CI: 76 to 93%, I^2=0%; 10 cohort studies, n=3,636) compared with non-outbreak settings (VE = 99%, 95% CI: 98 to 99%, I^2=34%; 2 cohort studies, n=83,560).[158] A second review that conducted a meta-analysis of studies in varicella clusters/outbreaks in China, reported a pooled VE, compared with no vaccination, of 92% (95% CI: 80 to 97%, I^2=0%; 3 studies).[169]

A total of four reviews that provided a narrative synthesis of findings reported VE against varicella of any severity for two-dose vaccination. Estimates of two-dose VE ranged from a pooled estimate of 92% (95% CI: 88 to 95%),[176] to two estimates of 98%, one of which 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]).[175] A narrative review of the experience in Germany reported results from one study that two-dose VE 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 of administration did not influence effectiveness.[88] Lastly, the review reported that VE 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).[88]

Figure 2.3 provides a summary of estimates of pooled two-dose VE 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.

Table 2.4 Summary characteristics for reviews that included two-dose varicella vaccination

Author and Year	Population	Vaccine type (brand)	Administered concurretly with another vaccine	Duration of follow-up	Main outcome	Type of synthesis	Authors overall conclusion	Risk of bias	Overall quality of evidence	AMSTAR 2 Rating for SR
Al Kaabi 2020[170]	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[171]	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[176]	Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy (associated systematic review based on the general population).	NR	NR	NR	VE 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

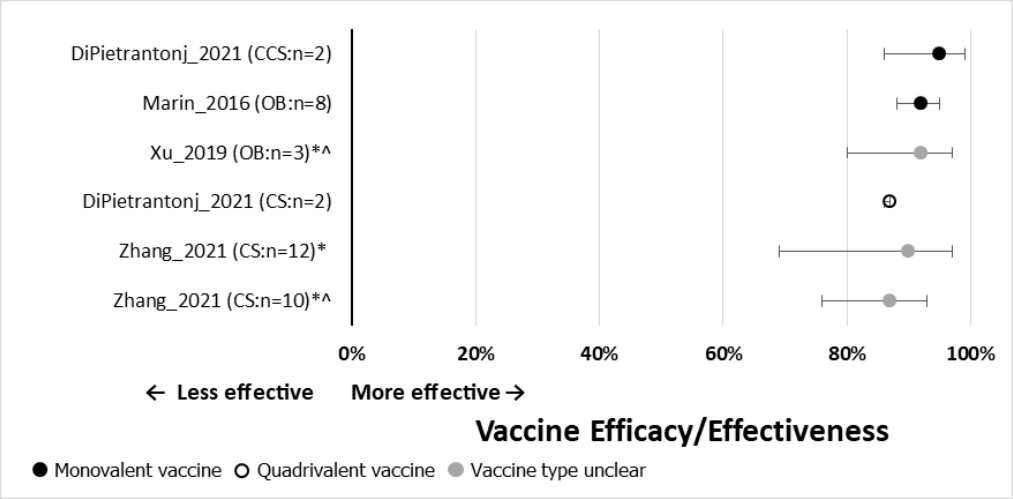
Author and Year	Population	Vaccine type (brand)	Administered concurretly with another vaccine	Duration of follow-up	Main outcome	Type of synthesis	Authors overall conclusion	Risk of bias	Overall quality of evidence	AMSTAR 2 Rating for SR
Di Pietrantonj 2021[159]	Healthy children aged up to 15yrs, or 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 VE against varicella	Meta-analysis	MMR+V and MMRV vaccines are effective in preventing the infection of children by chickenpox.	✓	✓	High
Garrido 2012[175]	Healthy children aged 1-12yrs at vaccination	NR	NR	Various	VE 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 possibility of two doses may be considered.	×	✓	Critically Low

Author and Year	Population	Vaccine type (brand)	Administered concurretly with another vaccine	Duration of follow-up	Main outcome	Type of synthesis	Authors overall conclusion	Risk of bias	Overall quality of evidence	AMSTAR 2 Rating for SR
Kaufmann 2020[88]	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 Germany: various including up to 10yrs post vaccination	VE against varicella including interval between vaccines and age at vaccination; Incidence of varicella; Hospitalised 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
Marin 2016[165]	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	VE 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. The second dose adds improved protection against all varicella.	×	×	Critically Low
New Zealand National Health Committee 2012[174]	Children aged 0-5yrs	NR	NR	Mostly NR: up to 10yrs post UVV introduction for hospitalised with varicella	VE against varicella; Hospitalised 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

Author and Year	Population	Vaccine type (brand)	Administered concurretly with another vaccine	Duration of follow-up	Main outcome	Type of synthesis	Authors overall conclusion	Risk of bias	Overall quality of evidence	AMSTAR 2 Rating for SR
Xu 2019[169]‡	Children and students in varicella clusters/ outbreaks in China	NR	NR	NR	VE against varicella	Meta-analysis	Varicella immunisation has a certain protective effect, which decreases with the increase of vaccination age.	×	×	Critically Low
Zhang 2021[158]	Healthy children aged 2-12yrs in China	NR except Beijing Tiantan Biological Products Corp. Ltd. (1 study)	NR	NR	VE against varicella	Meta-analysis	Available data from China showed that the VE of the two-dose varicella vaccine is relatively high.	✓	✓	Critically Low

Key:NR – not reported; SR – systematic review; UVV – universal varicella vaccination; VE – vaccine effectiveness

Figure 2.3 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).

Outcome: Efficacy/effectiveness in preventing moderate or severe varicella

Quadrivalent MMRV vaccine

The efficacy of two-dose quadrivalent MMRV vaccination in preventing moderate or severe varicella was reported in a single review: VE = 99% at 10 year follow-up (95% CI: 98 to 100%; 1 RCT, n=approx. 3,000; high-certainty evidence [GRADE] reported in review).[159]

Other outcomes

A limited number of reviews reported the impact of two-dose UVV and in most cases did not specify the vaccine type. In summary, varying reductions in incidence of varicella was reported in Germany,[88] regions of Italy[88] and in Abu Dhabi and Saudi Arabia,[170] following the introduction of two-dose UVV. Germany and Italy also reported reductions in hospitalisation associated with varicella, with the largest declines in Germany in those regions with the highest vaccination coverage.[88] In Puerto Rico, large reductions in rates of morbidity associated with varicella were reported in the period from two years after one-dose UVV introduction to eight years

after two-dose UVV introduction (monovalent vaccine).[171] These findings are summarised in **Table 2.5**.

Table 2.5 Findings from systematic reviews reporting the impact of two-dose universal varicella vaccination

Outcome	Vaccine type	Review	Country/ Region	Finding
Incidence of varicella	Mono OR Quad	Kaufmann 2020[88]	Germany	A three to four fold decrease in the incidence of varicella infection in Germany (from surveillance studies and other data sources) reported after the implementation of a 2-dose strategy.
		Kaufmann 2020[88]	Italy	Pooled analysis of epidemiological data from all eight Italian regions demonstrated significant reductions in incidence of varicella up to nine years after 2-dose UVV introduction.[88] In Sicily alone, varicella notifications decreased by over 95% between 2003 (when the 2-dose schedule was introduced) and 2012.[88]
		AlKaabi 2020[170]	Abu Dhabi, United Arab Emirates	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.
		AlKaabi 2020[170]	Saudi Arabia	Comparing pre- and post-UVV periods, incidence of varicella fell from 739.8 (1994) to 88.1 (2011) per 100,000 population (88% reduction) in Saudi Arabia.[170]
Morbidity	Mono	Arlant 2019[171]	Puerto Rico	Morbidity rates fell from 11.6 cases in 1998 to 2.8 cases per 100,000 population in 2015 (1 study).[171] The vaccination strategy changed from one-dose monovalent (introduced in 1996) to a 2-dose strategy from 2007; however, disaggregated data for the 1-dose strategy were not reported.
Varicella-related hospitalisation	Mono OR Quad	Kaufmann 2020[88]	Germany	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; 2-dose UVV introduced in 2009), with the highest declines observed in regions with the highest vaccination coverage.
		Kaufmann 2020[88]	Italy	Pooled analysis of epidemiological data from all eight regions of Italy that introduced 2-dose UVV from 2005, showed a substantial reduction in rates of hospitalisation associated with varicella by 2012.

2.4.3.3 Two- versus one-dose varicella vaccination

Three reviews assessed the efficacy/effectiveness of two- versus one-dose vaccination. A meta-analysis was conducted in two reviews,[160, 161] with a further review providing a narrative synthesis of findings.[175] All three reviews reported consistent findings of evidence that two-dose vaccination is more efficacious/effective in preventing varicella. The full findings have been provided in the supplementary material (**Appendix A 2.4**).

2.4.3.4 Any-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,[159, 169] with three further reviews providing a narrative synthesis of findings.[88, 163, 175] In addition to uncertainty around the number of doses, the vaccine type was also not clear in four of the five reviews.[88, 163, 169, 175] Given that the specific dosing schedule was not specified in these reviews, the usefulness of the results are limited in the context of assessing a suitable strategy for a UVV programme. Therefore the full findings regarding the effectiveness of 'any-dose' have been provided in the supplementary material (**Appendix A 2.5**).

2.4.4 Quality Appraisal

Quality appraisal was conducted independently by two reviewers using AMSTAR 2.[155] The majority of reviews had multiple methodological flaws with one review deemed 'high' quality,[159] one review deemed 'low' quality[88] and 18 reviews deemed 'critically low' quality.[158, 160-176] The 'high' quality review was a Cochrane Systematic Review, published in 2021.[159] 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. 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.[162-166, 169-176] In seven of the ten reviews that included a meta-

analysis of observational studies, it was not clear if estimates had been adjusted.[158, 161, 164, 166-169] The full set of results for the quality appraisal are provided in the supplementary file (**Appendix A 2.6**).

2.4.5 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.[167, 169] A total of 318 primary publications were identified, with 221 index publications (primary publications were counted on their first occurrence only).[156] The 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 CCA was calculated at 2.58, indicating slight overlap among index publications.[156]

2.5 Discussion

Overall, 20 systematic reviews that assessed the efficacy/effectiveness and impact of varicella vaccination were included in this overview of reviews. Although the majority of reviews contained multiple methodological flaws and only one review was deemed 'high' quality,[159] it is noted that there is substantial and consistent evidence underpinning the efficacy/effectiveness of varicella vaccination covering multiple strategies. The evidence base comprises 15 RCTs and 206 other primary studies/reviews conducted in non-specific settings as well as clusters/outbreaks, and where administered as part of UVV, with differing rates of vaccination coverage.

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,[159] to 88% effectiveness (follow-up period not reported).[168] In outbreak settings specifically, one-dose effectiveness ranged from 54% nine to 10 years after vaccination to 98% at less than three years after vaccination.[166] These estimates are supported from findings from reviews that provided a narrative synthesis of the effectiveness of one-

dose varicella vaccination.[88, 171, 174, 175] 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%.[159, 165, 174, 175]

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%,[159] with similar estimates for outbreak settings.[158, 169] These estimates were also supported by findings in additional reviews that reported two-dose VE in excess of 90% against varicella of any severity.[88, 174-176] The evidence on the efficacy/effectiveness of two-dose vaccination in preventing moderate and severe varicella was limited to a single review, but similar to one-dose vaccination was reported as highly effective (99% efficacy for two-dose quadrivalent MMRV vaccination) at 10 year follow-up post vaccination.[159]

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 moderate and severe disease with both strategies. However, 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.[88, 160, 161, 165] While VE appears to be lower in outbreak settings for one-dose strategies, possibly due to a higher force of infection in these settings (such as schools and childcare facilities), 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 included systematic reviews, the magnitude of effect for both dosing schedules is uncertain.

While there was evidence of waning, most notably against varicella of any severity for a one-dose strategy, there was still evidence of protection up to 10 years post vaccination; in the only review deemed 'high' quality, vaccine efficacy was estimated at 67% up to 10 years post vaccination.[159] Additionally, although many of the reviews (mostly one-dose strategies) did not report the age at which children were vaccinated, estimates of VE were higher in younger children compared with older children[167, 168] and higher six to eight years post-vaccination compared with nine to

ten years post-vaccination.[169] The evidence on the effectiveness of two-dose vaccination over time was limited, perhaps due to shorter follow-up periods given that two-dose strategies have been implemented more recently than one-dose strategies. However, the evidence available suggests less waning of immunity compared with one-dose strategies (98.3% VE over an observational period of up to 10 years post vaccination).[175] With respect to moderate or severe varicella, 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.[159]

The impact of varicella vaccination programmes on population-level incidence of varicella, and complications and hospitalisation associated with 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 vaccination programmes. Most reviews reported reduced incidence of varicella following the introduction of vaccination, and in countries that switched from one-dose to two-dose programmes, further decreases in incidence of varicella were reported following the change.[88] Similarly, there was evidence of reductions in varicella-related hospitalisations and complications associated with varicella following the introduction of one-dose vaccination, with further reductions in hospitalisations when a one-dose schedule was replaced with two doses.[88]

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. The evidence from the included reviews originates from many regions and countries, ensuring that the results are broadly generalisable. However, there are a number of important limitations. 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. None of the 'critically low' quality reviews included a published protocol or explicit statement that the review methods were established prior to the conduct of the review. Search strategies were not considered comprehensive in 15 reviews. 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 of the reviews. The source of evidence in 13 of the systematic reviews was solely observational, raising potential issues with bias and confounding. Of the ten reviews that included a meta-analysis, five were limited to studies conducted in China with potential implications for the generalisability of these data. Four of the reviews reported heterogeneity greater than 50% in the results of the meta-analyses conducted. While two of the reviews investigated the source of heterogeneity by conducting sub-group analyses and meta-regression, one review provided a possible explanation only and another reported that not all studies reported detail sufficient to enable a full analysis of the sources of heterogeneity. 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 on vaccine type administered, dosing-schedule, age at vaccination, and follow-up period after vaccination.

In assessing the potential introduction of a vaccination programme for a disease such as varicella that has a high reproduction number, vaccination uptake and the impact of uptake on programme effectiveness are important considerations. The reviews that examined the impact of UVV, either regionally or countrywide, reported limited data on vaccination coverage rates; where they were reported, they did not 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.[170] The lack of vaccination coverage data alongside corresponding outcome data, limits the

interpretation and understanding of the full impact of existing UVV programmes. Additionally, evidence gaps and the lack of detailed reporting on the effectiveness of two-dose quadrivalent vaccination against moderate/severe varicella, on VE based on age at vaccination, on VE based on interval between doses and immunity beyond 10 years post vaccination limit the ability to fully inform policy decisions where the introduction of UVV is being considered or where existing UVV programmes are under review. Despite the limitations and evidence gaps identified, this review provides strong evidence underpinning the efficacy/effectiveness of one- and two-dose childhood varicella vaccination strategies in preventing both varicella of any severity and moderate to severe varicella. Based on the evidence, a key consideration for policymakers on the possible introduction of a childhood varicella vaccination programme and the choice between a one- or two-dose strategy, will be whether the objective of a programme is to prevent varicella of any severity or to prevent moderate to severe varicella.

2.6 Conclusion

The aim of this overview of reviews was to establish the clinical efficacy and effectiveness of alternative varicella vaccination strategies by synthesising the evidence available from relevant systematic reviews that have been published to date. This overview has provided 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 both strategies have similar high efficacy/effectiveness in preventing moderate or severe varicella.

3 Safety of alternative varicella vaccination strategies: An overview of reviews

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3.1 Abstract

The safety of new vaccines under development as well as existing vaccines is a key priority for national and international public health agencies. A number of countries have implemented universal childhood varicella vaccination programmes over the past 30 years. However, strategies differ in terms of the number of doses, type of vaccine(s) recommended, age at vaccination and interval between doses for a two-dose schedule. An overview of reviews was undertaken to assess the existing systematic review evidence of the safety of varicella vaccination strategies. The review was restricted to immunocompetent children aged nine months to six years inclusive. A comprehensive search of databases, registries and grey literature was conducted up to 2 February 2022. Two reviewers independently screened, extracted data and assessed the methodological quality of included reviews. Overlap of included reviews was also assessed. A total of 17 reviews, incorporating both the monovalent varicella only and quadrivalent MMRV vaccines were included in the overview; six assessed the safety of one-dose strategies, four assessed the safety of two-dose strategies and 14 reviews did not specify the dosing strategy. The evidence suggests that mild local and systemic reactions are relatively common with varicella vaccination. Febrile seizures are also possible adverse effects of both the monovalent and quadrivalent MMRV vaccine, but serious adverse reactions are rare. While most reviews contained methodological flaws, and analysis by vaccine type and dosing strategy was restricted due to lack of detail in reporting of the reviews, there was clear and consistent evidence from a substantial evidence base, comprising 34 RCTs and 62 other primary studies/reviews, that varicella vaccination is safe.

3.2 Introduction

Varicella is a very common and highly contagious disease that typically affects children. Although usually mild, varicella may be associated with complications requiring hospitalisation.[11, 151] In the absence of universal vaccination, both the disease and economic burden of varicella are significant, with the latter driven by work productivity losses for caregivers.[11, 13, 24, 40] To combat VZV, a live attenuated vaccine for varicella was developed in the 1970s. The monovalent varicella vaccine was first licensed for universal routine vaccination of persons at least 12 months of age in the USA in 1995 and approval for the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine followed in 2005.[77, 88] In 2018, 23 years after a universal varicella vaccination (UVV) programme was first established in the USA, it was reported that 36 countries and regions globally had introduced UVV programmes for children.[90]

Vaccination is recognised as a key component of public health, helping to reduce or eliminate illness, prevent serious disease, improve life expectancy and save lives.[177] Vaccines are the most effective way to prevent and control infectious diseases and overall vaccines are estimated to save between 2 and 3 million lives per year.[178] The safety of both new vaccines under development and existing vaccines is thus a key priority for national and international public health agencies and is a prime concern in policy decisions regarding the implementation of new and the review of existing vaccination programmes.[7] Demonstrated safety through rigorous testing in clinical trials is required for initial market authorisation, and after trials have been conducted and a vaccine has been introduced, continuous monitoring is required to ensure that they remain safe for those who receive them during extended use.[5, 179] Additionally, demonstrated vaccine safety is critical to establish and maintain public trust in vaccines helping to ensure that vaccine uptake under national vaccination programmes is optimal and that these programmes are successful in achieving their objectives.[177]

The number of countries that have implemented UVV for children has steadily increased since the first programme was introduced almost thirty years ago. However, varying UVV strategies have been implemented over time and established programmes, both between and regionally within countries, differ in terms of the number of doses recommended (one or two), the type of varicella vaccine(s) recommended (monovalent, quadrivalent MMRV or both), the age at which the first dose is administered and the interval between doses where programmes include a two-dose schedule.[14, 152] A number of systematic reviews assessing the safety of varicella vaccines have been published over the last 40 years. However, early reviews are based on a one-dose monovalent vaccine schedule, while more recent reviews are based on both one- and two-dose schedules using both the monovalent and quadrivalent MMRV vaccines. No single existing systematic review captures the full range of possible vaccination strategies across multiple safety outcomes.

The aim of this overview of reviews was to assess the safety of varicella vaccination strategies, including both the monovalent and quadrivalent MMRV vaccines, and produce a comprehensive and comprehensible synthesis and summary of the evidence generated from existing systematic reviews.[180] In line with the recommended age for vaccination of many established universal childhood varicella vaccination programmes, the population of interest in this overview of reviews was restricted to immunocompetent children aged nine months to six years inclusive.

3.3 Methods

An overview of reviews was conducted in accordance with a pre-defined protocol that was registered on PROSPERO (registration number CRD42022312325).

3.3.1 Search strategy and selection of systematic reviews

A single search was conducted to retrieve systematic reviews on the efficacy, effectiveness and safety of varicella vaccination strategies, with the former outcome reported in a separate paper.[181] 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 an extensive grey literature search. All search strings, developed in consultation with an information specialist, dates of searches and search results are provided in the supplementary file (**Appendix A 3.1**). 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.

3.3.2 Data extraction and management

Titles and abstracts of potentially eligible reviews were screened independently by two reviewers using Covidence software.[154] Full text reviews were independently assessed for eligibility by two reviewers according to the pre-specified inclusion and exclusion criteria outlined in (**Table 3.1**). Data extraction 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.

Table 3.1 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 • alternative dosing schedule • alternative dosing interval • alternative age at vaccination • co-administration with another vaccine • no comparator.

Outcomes	**Safety**
	Any safety data including, but not limited to:
	• seizures/convulsions (febrile/afebrile)
	• anaphylaxis
	• disseminated vaccine-strain varicella zoster virus
	• encephalitis/encephalopathy
	• herpes zoster
	• pneumonia
	• meningitis
	• idiopathic thrombocytopenic purpura
	• hospitalisation for any effect of vaccination
	• short-term effects of vaccination:
	  ○ localised reactions at injection site (e.g., pain, redness, swelling)
	  ○ systemic reactions (e.g., fever, varicella-like rash, vomiting, diarrhoea)

Study design	**Include:**
	• reviews with the following key characteristics:
	  ○ a clearly stated set of objectives with an explicit, reproducible methodology
	  ○ a systematic search of at least two databases that attempts to identify all studies that would meet the eligibility criteria
	  ○ a systematic presentation, and synthesis, of the characteristics and findings of the included studies.
	• reviews reporting on at least one outcome of interest.
	
	Exclude:
	• reviews only reporting data on immunocompromised children
	• reviews only reporting data on persons ≥ seven years of age at vaccination
	• reviews that incorporate theoretical studies or text and opinion as their primary source of evidence
	• reviews that are published as an abstract only
	• eligible reviews that have been updated and the updated review is included.

3.3.3 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".[155] Disagreements were resolved by discussion and with third party arbitration, when required.

3.3.4 Data synthesis

Summary characteristics of included reviews and overall findings are presented in table format by vaccine dose. Findings that were extracted from the included reviews are synthesised narratively. The findings are presented by vaccine dose (one dose, two dose, one versus two dose, and unknown dose), safety outcome (tolerance, local adverse events, systemic adverse events, serious adverse events, febrile seizures, and other safety outcomes) and vaccine type (monovalent, quadrivalent MMRV and monovalent or quadrivalent MMRV [where the vaccine type was not specifically reported]). The term tolerance has a broad interpretation as the underlying reviews did not provide a clear or consistent definition. Local adverse events included pain, redness and swelling at the injection site. Systemic adverse events included fever and rash. Summary output figures were developed where appropriate.

3.3.5 Overlap of included reviews

Overlaps of original research studies in each of the included reviews were identified where possible. The overall 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.[156] A CCA of 0-5 indicates slight overlap, 6-10 moderate overlap, 11-15 high overlap and >15 very high overlap. [156]

3.3.6 Reporting

The reporting of this overview of reviews adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.[157]

3.4 Results

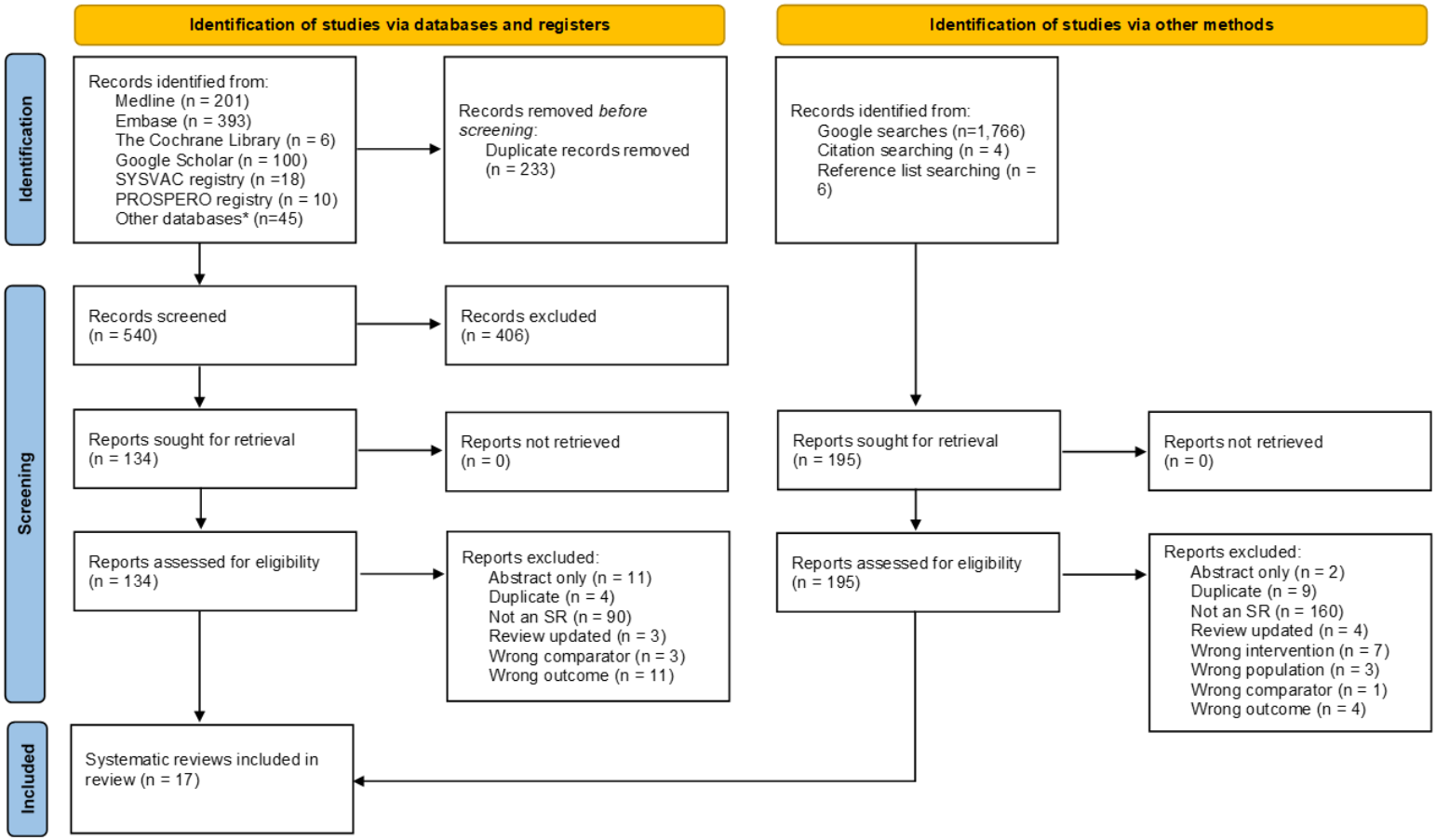
3.4.1 Search findings

After removing duplicates, the initial search (for efficacy, effectiveness and safety studies) 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 (efficacy, effectiveness and safety) 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 (**Appendix A 3.2**), 13 systematic reviews remained for inclusion in this overview of reviews (n=12 from databases, registers and grey literature sources and n=1 from Google). An additional ten reviews were identified from reference checking and forward citation searching of included reviews, four of which were deemed eligible for inclusion, giving a final total of 17 eligible systematic reviews (**Figure 3.1**).

3.4.2 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.[182] Of the 17 reviews, one review included randomised controlled trials (RCTs) only,[183] six reviews included RCTs and observational studies[162, 175, 176, 182, 184, 185] of which one also included two previously published systematic reviews,[175] two included RCTs and other study types that were unclear,[163, 174] five included observational studies only, [159, 160, 186-188] two included case reports only[189, 190] and the study types were not clear in one review.[191] Of the two systematic reviews that were themselves included in an eligible systematic review for this overview,[175] neither met the pre-defined eligibility criteria (**Table 3.1**) 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.

Figure 3.1 PRISMA 2020 flow diagram of included studies



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

Four of the 17 reviews that assessed safety provided a meta-analysis,[159, 160, 183, 185] two of which included a meta-analysis of RCT data.[183, 185] The remaining thirteen reviews provided a narrative summary of findings.[162, 163, 174-176, 182, 184, 186-191] None of the 17 reviews had a geographic limitation. Completed data extraction tables for all included reviews are provided in the supplementary file (**Appendix A 3.3**).

3.4.3 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 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). **Table 3.2** and **Table 3.3** provide an overview of the characteristics of included systematic reviews by safety outcome and specific adverse event.

Table 3.2 Overview of systematic reviews of safety of varicella vaccination by safety outcome (general)

Safety outcome	Review	Dose	Type of vaccine	Type of studies	Type of analysis	Date of last search
Tolerance	NZ_2012[174]	2-dose	Quadrivalent	RCT	NS	Nov 2011
	Ma_2015a[183]	2-dose	Quadrivalent	RCT	NS	Sep 2014
	NZ_2012[174]	Unknown-dose	Quadrivalent	RCT	NS	Nov 2011
	NZ_2012[174]	Unknown-dose	Unclear	Unclear	NS	Nov 2011
Reactions	Skull_2001[162]	2- v 1-dose	Unclear	Unclear	NS	Dec 2000
Local adverse events (pain, redness, swelling)	Pallas_2011[163]	1-dose	Monovalent and quadrivalent	RCT and feasibility	NS	Unclear (2010/2011)
	Ma_2015a[183]	1-dose	Quadrivalent	RCT	NS	Sep 2014
	Yin_2018[160]	2- v 1-dose	Quadrivalent	Self-controlled	MA	Jun 2017
	Ma_2015a[183]	2- v 1-dose	Quadrivalent	RCT	NS	Sep 2014
	Skull_2001[162]	Unknown-dose	Unclear	RCT and others	NS	Dec 2000
	NZ_2012[174]	Unknown-dose	Unclear	Unclear	NS	Nov 2011
	Garrido_2012[175]	Unknown-dose	Unclear	RCT	NS	Nov 2009
Systemic adverse events (fever, rash)	Pallas_2011[163]	1-dose	Monovalent	RCT	NS	Unclear (2010/2011)
	Ma_2015a[183]	1-dose	Quadrivalent	RCT	NS	Sep 2014
	Pallas_2011[163]	2-dose	Monovalent and quadrivalent	RCTs and review	NS	Unclear (2010/2011)
	Yin_2018[160]	2- v 1-dose	Monovalent and quadrivalent	Self-controlled	MA	Jun 2017
	Pallas_2011[163]	2- v 1-dose	Quadrivalent	RCT	NS	Unclear (2010/2011)
	Bauwens_2019[184]	Unknown-dose	Monovalent co-administered with other vaccines	RCT	NS	Jan 2019
	Skull_2001[162]	Unknown-dose	Unclear	RCT	NS	Dec 2000
	Pallas_2011[163]	Unknown-dose	Unclear	RCT	NS	Unclear (2010/2011)
	NZ_2012[174]	Unknown-dose	Unclear	Unclear	NS	Nov 2011
	Garrido_2012[175]	Unknown-dose	Unclear	RCT	NS	Nov 2009
Adverse events	Pallas_2011[163]	1-dose	Monovalent	RCT	NS	Unclear (2010/2011)
	Ma_2015a[183]	1-dose	Quadrivalent	RCT	NS	Sep 2014
	Garrido_2012[175]	1-dose	Unclear	SR	NS	Nov 2009
	Pallas_2011[163]	2- v 1-dose	Quadrivalent	RCT	NS	Unclear (2010/2011)
	Bauwens_2019[184]	Unknown-dose	Monovalent co-administered with other vaccines	RCT	NS	Jan 2019
	Bauwens_2019[184]	Unknown-dose	Quadrivalent co-administered with other vaccines	RCT	NS	Jan 2019

Safety outcome	Review	Dose	Type of vaccine	Type of studies	Type of analysis	Date of last search
	NZ_2012[174]	Unknown-dose	Quadrivalent co-administered with other vaccines	Unclear	NS	Nov 2011
	Benchimol_2011[176]	Unknown-dose	Unclear	RCT, observational and post-licensure	NS	Apr 2019
	Skull_2001[162]	Unknown-dose	Unclear	RCT and post-licensure	NS	Dec 2000

Key: MA – meta-analysis; NS – narrative synthesis; PTCS – person time cohort study; RCT – randomised controlled trial; SCCS – self-controlled case series; SR – systematic review.

Table 3.3 Overview of systematic reviews of safety of varicella vaccination by specific adverse event

Safety outcome	Review	Dose	Type of vaccine	Type of studies	Type of analysis	Last date of search
Acute disseminated encephalomyelitis	Gidengil_2021[182]	Unknown-dose	Monovalent and quadrivalent	Unclear	NS	Nov 2020
Anaphylaxis/systemic allergic reaction	Gidengil_2021[182]	Unknown-dose	Monovalent and quadrivalent	Unclear	NS	Nov 2020
Arthritis or arthralgia	Panozzo_2019[187]	Unknown-dose	Unclear	Cohort	NS	Unclear (Dec 2017)
Arthropathy and cytopenia	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
Ataxia	Gidengil_2021[182]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2020
Death	Ma_2015a[183]	1-dose	Quadrivalent	SR	NS	Sep 2014
	Skull_2001[162]	1-dose	Unclear	RCT and post-licensure	NS	Dec 2000
	Gidengil_2021[182]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2020
	NZ_2012[174]	Unknown-dose	Unclear	Unclear	NS	Nov 2011
	Garrido_2012[175]	Unknown-dose	Unclear	Observational	NS	Nov 2009
	Skull_2001[162]	1-dose	Unclear	RCT and post-licensure	NS	Dec 2000
Disseminated Oka VZV without other organ involvement	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
Gastroenteritis	Garrido_2012[175]	Unknown-dose	Unclear	RCT	NS	Nov 2009
Guillain-Barré syndrome	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
Herpes zoster	NZ_2012[174]	1-dose	Unclear	Various	NS	Nov 2011
	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
	Skull_2001[162]	Unknown-dose	Unclear	RCT, cohort, surveillance	NS	Dec 2000
Idiopathic thrombocytopenic purpura	VandenBoogaard_2021[190]	Unknown-dose	Monovalent	Case report	NS	Nov 2011
	Gidengil_2021[182]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2020
	DiPietrantonj_2021[159]	Unknown-dose	Quadrivalent	SCCS	MA	May 2019
	Garrido_2012[175]	Unknown-dose	Unclear	RCT	NS	Nov 2009
Kawasaki disease	Gidengil_2021[182]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2020
	Phuong_2017[188]	Unknown-dose	Quadrivalent	Cohort	NS	Jun 2016
Laryngospasm	Garrido_2012[175]	Unknown-dose	Unclear	RCT	NS	Nov 2009
Meningitis	Gidengil_2021[182]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2020
Pneumonia	Garrido_2012[175]	Unknown-dose	Unclear	RCT	NS	Nov 2009
Seizure including febrile	Ma_2015b[185]	1-dose	Quadrivalent	RCT	MA	Dec 2014

Safety outcome	Review	Dose	Type of vaccine	Type of studies	Type of analysis	Last date of search
seizure	Ma_2015a[183]	1-dose	Quadrivalent	RCT	NS	Sep 2014
	Ma_2015b[185]	2-dose	Quadrivalent	RCT	MA	Dec 2014
	Ma_2015b[185]	2-dose	Quadrivalent co-administered with other vaccines	RCT	MA	Dec 2014
	DiPietrantonj_2021[159]	Unknown-dose	Monovalent and quadrivalent	SCCS/PTCS	MA	May 2019
	VandenBoogaard_2021[190]	Unknown-dose	Quadrivalent	Case report	NS	Nov 2011
	Gidengil_2021[182]	Unknown-dose	Monovalent and quadrivalent	Unclear	NS	Nov 2020
	Ma_2015b[185]	Unknown-dose	Quadrivalent	Cohort & matched cohort	MA	Dec 2014
	Gidengil_2021[182]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2020
	NZ_2012[174]	Unknown-dose	Quadrivalent	Unclear	NS	Nov 2011
Sixth nerve palsy	VandenBoogaard_2021[190]	Unknown-dose	Monovalent	Case report	NS	Nov 2011
Small fibre neuropathy	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
Stevens Johnson Syndrome	Grazina_2020[189]	Unknown-dose	Unclear	Case report	NS	Feb 2018
Transverse myelitis	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
Unsolicited adverse event - pharyngitis	Ma_2015a[183]	1-dose	Quadrivalent	SR	NS	Sep 2014
Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis	Gidengil_2021[182]	Unknown-dose	Monovalent	Unclear	NS	Nov 2020
Varicella reactivation meningitis	Amaral_2021[191]	Unknown-dose	Unclear	Case report	NS	Jun 2020
Varicella transmission from vaccinated individuals	Skull_2001[162]	Unknown-dose	Unclear	RCT and case report	NS	Dec 2000
vOka transmission	Marin_2019[186]	1-dose	Unclear	NR	NS	Dec 2018

Key: MA – meta-analysis; NR – not reported; NS – narrative synthesis; RCT – randomised controlled trial; SCCS – self-controlled case series.

3.4.3.1 One-dose varicella vaccination

A total of six reviews assessed the safety of one-dose varicella vaccination ,[162, 163, 174, 183, 185, 186] with two reviews providing a meta-analysis[183, 185] and four reviews providing a narrative synthesis of findings.[162, 163, 174, 186] Safety outcomes for one dose included local adverse events, systemic adverse events, adverse events (including serious adverse events [SAEs]), febrile seizures, and a number of other safety outcomes. A narrative summary of results by safety outcome measure and vaccine type is provided below.

Outcome: local adverse events

Monovalent vaccine

A higher incidence of injection-site adverse events at varicella vaccine injection sites than at measles mumps rubella (MMR) injection sites were reported in one review (2 RCTs).[163] 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.[163] 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.[163]

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).[183] A further review reported no difference in the frequency of local adverse events between recipients of MMRV and MMR vaccines (2 RCTs).[163]

Outcome: systemic adverse events

Monovalent vaccine

A single review reported no difference in incidences of fever and rash between recipients of separate MMR and varicella vaccines (MMR+V) and recipients of MMR only (3 RCTs), with rashes reported very infrequently.[163] In the same review, a further two RCTs reported slightly higher incidence of fever in recipients of MMR+V than in recipients of MMR.[163] 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.[163]

Quadrivalent MMRV vaccine

A single review reported that irrespective of follow-up period (0-15 days or 0-42 days after vaccination), significantly higher incidences of fever (any) were reported in the 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]; 5 RCTs) after one-dose; 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.[183] 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; 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.[183]

Outcome: 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).[183]

Outcome: 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).[185] 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).[185] 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).[183]

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.[185]

Outcome: other safety outcomes

A number of additional safety outcomes were reported for one-dose vaccination. The outcomes included death (two reviews),[162, 183] herpes zoster (one review),[174] unsolicited adverse events (one review),[23] and vaccine strain varicella transmission from a vaccine recipient (one review).[186] The findings for these outcomes are presented in **Table 3.4**.

Table 3.4 Additional safety outcomes and findings reported for one-dose varicella vaccination

Safety outcome	Vaccine	Review	Review Findings
Death	Quadrivalent MMRV	Ma_2015[183]	No related fatal serious adverse event was reported in any studies (5 RCTs) in the review.
	Unclear	Skull_2001[162]	No deaths have been reported for subjects in either vaccine or placebo groups for controlled varicella vaccine

Safety outcome	Vaccine	Review	Review Findings
			trials. A post-licensure study included in the review 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.
Herpes zoster	Quadrivalent MMRV	NZNHC_2021[174]	At an individual study level, most studies suggest that the risk of HZ following a single dose quadrivalent MMRV vaccination is lower than the risk following wild-type varicella infection
Unsolicited adverse events	Quadrivalent MMRV	Ma_2015[183]	15 pre-specified unsolicited adverse events from three RCTs were examined; 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.
vOka (vaccine strain varicella) transmission from vaccine recipient	Unclear	Marin_2019[186]	Of 12 case reports of vOka transmission from varicella vaccine recipients: ▪ 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. ▪ Five confirmed cases of vOka transmission from a vaccine recipient (one confirmed MMRV) with HZ were reported, with secondary cases developing a rash, lesions or fever within 14 to 19 days after HZ onset in the index case. ▪ 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. 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.

Key: MMRV – measles, mumps, rubella, varicella; RCT – randomised controlled trial; RR – relative risk; vOka – vaccine strain varicella.

3.4.3.2 Two-dose varicella vaccination

A total of four reviews assessed the safety of two-dose varicella vaccination,[163, 174, 183, 185] with two reviews providing a meta-analysis,[183, 185] and two reviews providing a narrative synthesis of findings.[163, 174] Safety outcomes for two doses included vaccine tolerance, systemic adverse events, adverse events (including SAEs) and febrile seizures. A narrative summary of the results by safety outcome measure and vaccine type is provided below.

Outcome: 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).[174] 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.[183]

Outcome: systemic adverse events

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).[163] 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).[163] However,

incidence of fever after the second dose did not differ between groups (3 RCTs, 1 review).[163]

Outcome: 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+V (75.6%) and MMR alone (78.0%), with no vaccine-related serious adverse experiences reported.[163]

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).[163]

Outcome: 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].[185] 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].[185]

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).[185]

3.4.3.3 Two- versus one-dose varicella vaccination

A total of four reviews assessed the safety of two- versus one-dose varicella vaccination,[160, 162, 163, 183] with one review providing a meta-analysis[160] and three reviews providing a narrative synthesis of findings.[162, 163, 183] Safety outcomes for two doses versus one dose included reactions, local adverse events and systemic adverse events. A narrative summary of results by safety outcome measure and vaccine type is provided below.

Outcome: reactions

Monovalent or quadrivalent MMRV 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).[162]

Outcome: local adverse events

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.[160] 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.[160] 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.[160] 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.[160] 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).[183] 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).[163]

Outcome: systemic adverse events

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.[160]

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.[160] 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.[160] 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.[160] 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).[160] An earlier review reported that overall incidence of systemic adverse events was similar among recipients of one- and two-dose MMRV vaccination (3 RCTs).[163]

3.4.3.4 Unknown varicella vaccination dose

A total of fourteen reviews that assessed the safety of varicella vaccination did not specify the number of vaccine doses.[159, 162, 163, 174-176, 182, 184, 185, 187-191] Two reviews that assessed the quadrivalent vaccine conducted a meta-analysis,[159, 185] while all

other reviews provided a narrative synthesis of findings. Where the number of vaccine doses was unknown, safety outcomes included vaccine tolerance, local adverse events, systemic adverse events, seizures and febrile seizures, and a number of other safety outcomes including SAEs. A narrative summary of results by safety outcome measure and vaccine type is provided below.

Outcome: 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).[174]

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.[174]

Outcome: local adverse events

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 7–30% of study participants.[162] A second review noted international experience suggesting that local reactions to the varicella vaccine are possible.[174]

Outcome: systemic adverse events

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.[184] 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).[184]

Monovalent or quadrivalent MMRV 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).[162] 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).[163] In the same review, the incidence of fever following MMR+V or MMRV vaccination was higher than following MMR vaccination (2 RCTs).[163] Another review, conducted at the same time, noted international experience suggesting that fever and mild papulovesicular rash are possible adverse effects of the vaccine.[174] 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.[175] 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.[175]

Outcome: 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] reported in review).[159]

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] reported in review).[159] 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]) reported in review 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]) reported in review at 0-42 days after vaccination.[159] 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.[185] In the same review, similarly an approximate 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.[185] 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).[185] The third review reported insufficient evidence to assess the risk of seizures with the quadrivalent (ProQuad®) vaccine.[182] The fourth review noted international experience suggesting that febrile seizures are possible adverse effects of the quadrivalent MMRV vaccine.[174] A final review, assessing the safety of rubella-containing vaccines, reported a single case of a 13 month old girl with high fever one day after MMRV vaccination and seizures six days later.[190]

Outcome: other specific safety outcomes and serious adverse events

A number of reviews that didn't specify the number of vaccine doses reported other specific safety outcomes and serious adverse events. The findings for these outcomes are presented in **Table 3.5**.

Table 3.5 Additional safety outcomes and findings reported for unknown dose varicella vaccination

Safety outcome	Vaccine	Review	Review Findings
Various	Monovalent	Gidengil_2021[182]	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 the 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. However, estimates of the magnitude of increased risk were not determined. The review reported insufficient SoE of increased risk of the following adverse events associated with the monovalent varicella vaccine: • seizures • acute disseminated encephalomyelitis • transverse myelitis • Guillain-Barré syndrome • small fibre neuropathy • onset or exacerbation of arthropathy and thrombocytopenia.
Adverse events	Monovalent vaccine co-administered with another vaccine	Bauwens_2020[184]	No statistically significant difference in adverse events between co-administration and separate administration of the monovalent varicella vaccine and MMR vaccine (3 RCTs).
Temporary sixth nerve palsy Thrombocytopenic purpura		VandenBoogaard_2021[190]	In assessing the safety of rubella-containing vaccines, this review reported: • a case with first episode of temporary sixth nerve palsy after MMR vaccination and a second episode after varicella vaccination. • 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.
Kawasaki Disease	Quadrivalent MMRV	Phuong_2017[188]	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.
Thrombocytopenic purpura		DiPietrantonj_2021[159]	Rate ratio for idiopathic thrombocytopenic purpura of 2.87 (95% CI: 0.78 to 10.56; 1 self-controlled case series) for the MMRV vaccine (versus no vaccination) for children aged nine to 23 months.

Safety outcome	Vaccine	Review	Review Findings
Various		Gidengil_2021[182]	Reported no increased risk (low SoE based on the USA AHRQ Evidence-based Practice Center grading) associated with the quadrivalent (ProQuad®) vaccine for acute disseminated encephalomyelitis and death. 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.
Adverse events	Quadrivalent MMRV vaccine co-administered with another vaccine	Bauwens_2020[184]	No statistically significant difference in adverse events between co-administration and separate administration for a number of vaccines (see Supplementary File – **Appendix A 3.4**).
Nasopharyngitis		Bauwens_2020[184]	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)
General safety profile		New Zealand National Health Committee_2012[174]	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 conjugate vaccine (PHiD-CV) vaccine does not compromise the safety profile of either vaccine (2 RCTs).
Arthritis or arthralgia	Unclear	Panozzo_2019[187]	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.
Death		New Zealand National Health Committee_2012[174]	There do not appear to be any reported deaths due to the varicella vaccine.
		Garrido_2012[175]	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.
Herpes zoster		Skull_2001[162]	A single RCT reported no cases of HZ 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. 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

Safety outcome	Vaccine	Review	Review Findings
			cases/100,000 person-years for school-aged children following natural chickenpox. The review also included data from the USA 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).
Serious adverse events		Skull_2001[162]	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
		Garrido_2012[175]	Four serious adverse events were reported after varicella vaccination (1 RCT): idiopathic cytopenic thrombus purpura, gastroenteritis, pneumonia and laryngospasm. The study concluded that the vaccine is safe and has a good tolerability profile in children aged 12-15 months.
		Benchimol_2021[176]	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]).
Stevens Johnson Syndrome		Grazina_2020[189]	An assessment of 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). The review concluded that a causal link between vaccination and SJS cannot be established by this study.
Varicella reactivation meningitis		Amaral_2021[191]	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.
Varicella transmission from vaccinated individuals		Skull_2001[162]	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.

Key: AHRQ – Agency for Healthcare Research and Quality; HZ – herpes zoster; KD – Kawasaki Disease; MMR – measles, mumps, rubella; MMRV – measles, mumps, rubella, varicella; PCV7 - pneumococcal conjugate vaccine seven-valent; PHID-CV - pneumococcal haemophilus influenzae protein D conjugate vaccine; RCT – randomised controlled trial; RD – risk difference; RR – relative risk; SJS –Stevens Johnson syndrome; SoE – strength of evidence; VZV – varicella zoster virus.

3.5 Quality Appraisal

The majority of reviews had multiple methodological flaws with one review deemed 'high' quality,[159] two reviews deemed 'low' quality[182, 189] and 14 reviews deemed 'critically low' quality.[160, 162, 163, 174-176, 183-188, 190, 191] 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.[160, 162, 163, 174-176, 182-184, 186-191] A list of excluded studies and reasons for exclusions were provided for three reviews only.[159, 163, 182] Included studies were fully described in adequate detail in four reviews only.[159, 163, 185, 187] 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.[163, 174-176, 184, 186-188, 191] The full set of results for the quality appraisal are provided in the supplementary file **Appendix A 3.5**.

3.6 Overlap within included reviews

Overlap calculations were calculated based on 16 reviews, as primary publications were not identifiable in one review.[160] Although RCTs were not identifiable in another review, the review was included in overlap calculations as other primary studies/reviews were identifiable.[185] 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).[156] 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 among index publications.[156]

3.7 Discussion

A total of 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,[159] it is noted that there is substantial evidence underpinning the safety of varicella vaccination, comprising 34 RCTs and 62 other primary studies/reviews.

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 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. Given that the search also included reviews of clinical efficacy/effectiveness, reviews including studies primarily designed to establish vaccine efficacy/effectiveness but with additional safety data, which may not have been identified in a search for safety reviews only, are included. The evidence from the included reviews originates from many regions and countries across the globe, ensuring that the results are broadly generalisable.

Overall, the evidence suggests that some local reactions (typically mild) are possible after one- and two-dose monovalent and quadrivalent vaccination. 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.[162, 163] Additionally, the relative risk for systemic adverse events may be lower after the second dose (both monovalent and quadrivalent) compared with the first dose.[160] 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).[159] RCT data from one review 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.[185] However, in two further reviews where the dosage was not specified,[159, 185] the observational evidence, deemed 'low certainty' in one review,[159] suggests a greater risk of seizure/febrile seizures after MMRV vaccination compared with MMR vaccination alone. Overall, the evidence suggests that febrile seizures are possible adverse effects of both the monovalent and quadrivalent MMRV vaccine.

With regard to 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.[182] On the risk of herpes zoster, the evidence was mixed with one review reporting low case numbers (vaccine type not specified)[162] and a second 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.[174] A number of observational studies conducted in the US during the varicella vaccination era support the finding of a lower risk of herpes zoster following wild type versus vaccine strain varicella infection.[192-194] A number of reviews provided case reports of specific rare, serious adverse events following varicella vaccination. These adverse events included arthritis/arthralgia,[187] Kawasaki Disease,[188] Stevens Johnson Syndrome,[189, 191] and varicella reactivation meningitis,[170] with no association with varicella vaccine (monovalent or quadrivalent) reported.

There are a number of important limitations to the review. The quality of the reviews included in this overview was largely deemed 'critically low'. With the exception of one review,[159] 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 (including 34 RCTs) could not be ascertained as risk of bias assessments were not

conducted for many reviews. The source of evidence in half of the systematic reviews was solely observational, raising potential issues with bias and confounding. With regard to serious adverse events specifically, it should be noted that RCTs are generally underpowered to detect differences in these rates between groups given the rarity of these events, while observational studies are often not suitable for determining a difference between groups. As an overview of reviews, this study examined systematic reviews, rather than the original studies, and therefore some of the detail from the original papers may have been lost and any primary studies published since the last review have not been included. A final limitation of this review is that the population of interest was restricted to those aged nine months to six years. While there may be additional evidence associated with vaccination in older age groups, existing national childhood varicella immunisation programmes typically administer the vaccine by six years of age, and the majority of varicella incidence occurs in younger children.

There were 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 on vaccine type administered, the number of vaccine doses, age at vaccination, and follow-up period after vaccination. 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. While the under-reporting of absolute risk of adverse events also limits the ability to draw conclusions regarding the overall burden of adverse events, the majority of reviews highlighted that the vaccine(s) were well tolerated and that serious adverse reactions were rare. There were also a number of evidence gaps in the literature particularly with regard to limited evidence on the co-administration of the varicella vaccine with other vaccines. From a policy perspective, the lack of detailed reporting and evidence gaps can 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.

3.8 Conclusion

The aim of this overview of reviews was to establish the clinical safety of varicella vaccination strategies by synthesising the evidence available from relevant systematic reviews that have been published to date. This overview has provided clear and consistent evidence that both monovalent varicella and quadrivalent MMRV vaccination are safe. While the evidence suggests that mild local and systemic reactions, such as fever and rash, are relatively common, and that febrile seizures are possible adverse effects of both the monovalent and quadrivalent MMRV vaccine, it also suggests that serious adverse reactions are rare. The safety data support current recommendations for varicella vaccination but ongoing surveillance to monitor the safety of varicella vaccines is still needed.

4 A rapid review of methodology for the economic modelling of childhood varicella vaccination

4.1 Introduction

The availability of comprehensive guidelines or frameworks on how best to conduct economic evaluations of vaccines has been described as scarce.[195] In response, a consensus framework for economic evaluation of vaccines was developed to support the development of national guidelines in Europe. The 13 specific considerations identified, 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.[195]

With respect to economic modelling for infectious diseases, two of these considerations, namely model selection and perspective adopted, are the subject of specific discussion in the literature. A number of studies have highlighted the importance of adopting the most appropriate model to support economic evaluations of infectious disease interventions.[132, 196-198] Given the communicable nature of many infectious diseases, where the force of infection can change over time, appropriate model choice ensures the complexities of the disease can be accounted for. A number of studies have published flow diagrams to aid modellers

in selecting the most appropriate model for the economic evaluation of infectious disease interventions.[132, 198] In terms of the perspective adopted in economic evaluations, national guidelines for conducting economic evaluation, including those for Ireland,[130] generally focus on the payer perspective for the 'reference case' or in the base case scenario. However, it is argued that for interventions for communicable infectious diseases, where there are possible impacts on individuals and wider society, beyond those vaccinated, the perspective should be broadened.[198-200]

In addition to methodological considerations for the economic evaluation of health technologies, identifying appropriate evidence is also an essential element of economic evaluation.[135] This applies to parameters relating to the effectiveness and safety of interventions, as well as resource use and the associated costs, and health-related quality-of-life weights. It is rare that all relevant evidence and data will come from a single source. Therefore, it will typically be drawn from multiple diverse sources, including various national and international sources as required and available. [135, 201] As such, economic modelling studies generally carry a heavy data burden. Economic models generally reflect the evidence base, both in terms of model structure and model input data, at the time that an economic evaluation is conducted. As knowledge develops and evolve over time, so too do the economic models.

To inform the development of a de novo economic model for evaluating the cost effectiveness of universal childhood varicella vaccination in Ireland, this chapter reviews the published international evidence on modelling for economic evaluations of childhood varicella vaccination. The review specifically examines the approaches taken to modelling the expected costs and benefits, incorporating model structure and input parameters, with consideration of the specific items identified in the consensus framework noted above.[195]

4.2 Methods

A scoping exercise was initially 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,[202-206] with heterogeneity observed in a number of aspects of the included economic evaluations, including the type of model, the perspective adopted, modelling of waning immunity, assessment of indirect costs, modelling the effect of varicella vaccination on herpes zoster, and estimation of the efficacy parameters.[203, 205, 206] The most recent systematic review (referred to hereafter as the '2015 systematic review' or 'earlier 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.[205] Studies conducted in high-income countries are more 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.[a] 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 in the 2015 systematic review)

[a]A protocol for a systematic review of the cost effectiveness of varicella vaccination programmes was identified on PROSPERO during the scoping stage of this review.[141]
The authors were contacted and confirmed that the systematic review was ongoing. As the two reviews were similar and the results of the systematic review were published in 2023, this rapid review was not submitted for publication.[142]

to June 2022. The results from the rapid review were combined with those from the 2015 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.

4.2.1 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 4.1).

Table 4.1 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 childhood varicella vaccination, including, but not limited to:
	• Model structure
	  ○ Type of model
	  ○ Perspective adopted
	  ○ Time horizon
	  ○ Age at vaccination
	  ○ Dosing schedule
	  ○ Vaccine type
	  ○ Comparator
	  ○ Waning immunity
	• Model input parameters
	  ○ Vaccine efficacy or effectiveness
	  ○ Vaccination coverage
	  ○ Direct and indirect costs
	  ○ Direct and indirect effects
	  ○ Utility values for cost-utility analysis
	• Model outputs
	  ○ Economic results that include a ratio of (incremental) costs to (incremental) benefits.

Context	Universal childhood varicella vaccination programmes in high income countries[‡]

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

4.2.2 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. As the intervention under consideration is a universal vaccination programme, studies relating to targeted vaccination of immunocompromised people, adolescents and or adults, or healthcare workers were not eligible for inclusion.

4.2.3 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 2015 systematic review.[205] The database search strings, developed in consultation with an information specialist, dates of searches and search results are provided in **Appendix A 4.1** and are publicly available on Zenodo via this link.

4.2.4 Study selection, data extraction and management

Results were exported to Covidence software[154] 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 4.1 and section 4.2.2. 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.

4.2.5 Data extraction and quality appraisal

Table 4.2 details the data that were extracted for each included study. In line with the 2015 systematic review,[205] critical appraisal of all included studies was

undertaken using the framework for quality assessment of decision-analytic models proposed by Philips et al.[207] The framework assesses the quality of models under three key themes; Structure, Data and Consistency.

4.2.6 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 2015 systematic review 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.[157]

Table 4.2 Data extracted from each included study

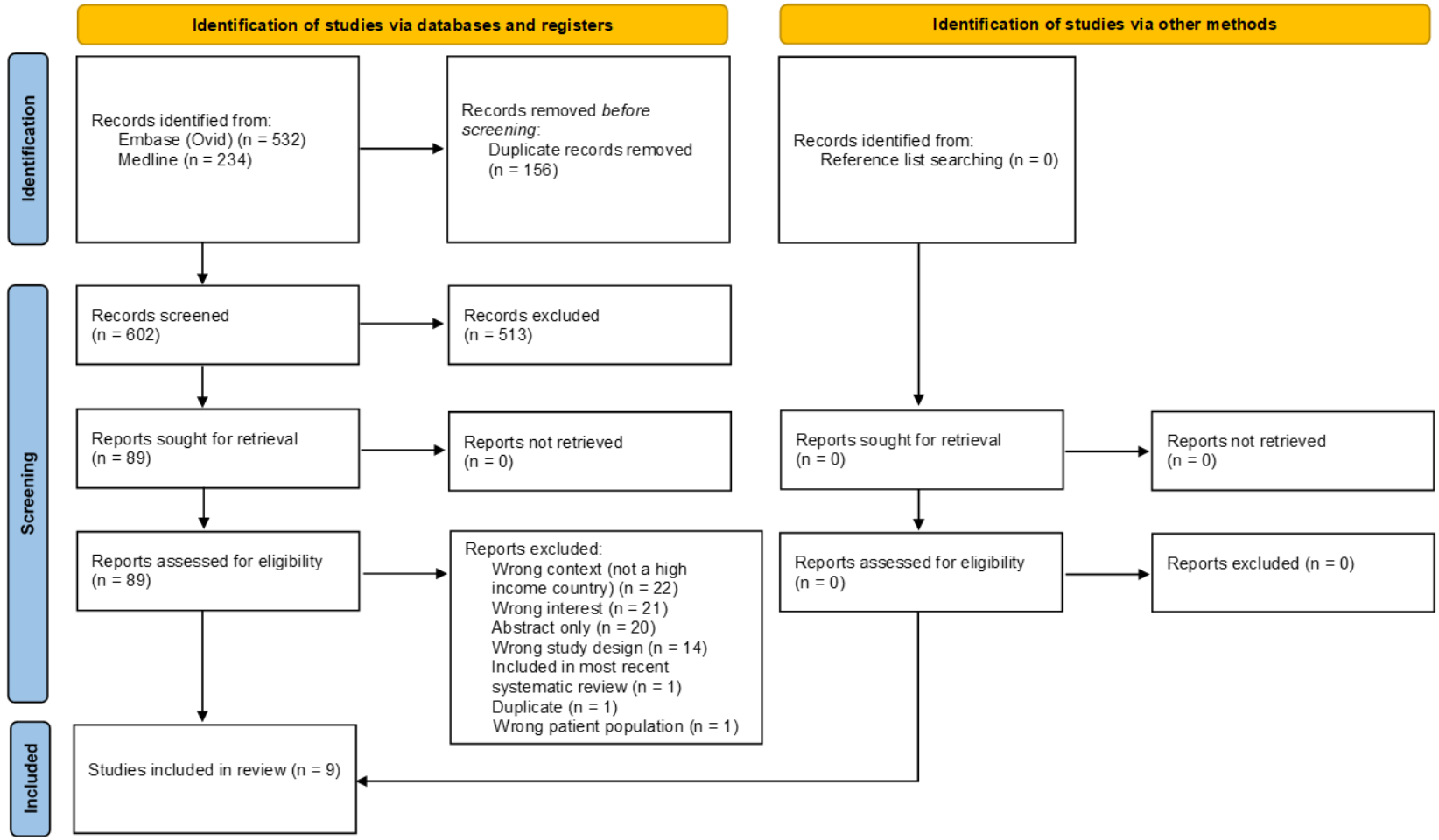
General study characteristics	• author name • year of publication • country • type of economic evaluation • population • funding source
Model characteristics	• model type • perspective • time horizon • comparator • discount rates for costs and outcomes
Intervention and vaccination strategy	• vaccine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

	• overall healthcare perspective result • overall societal perspective result • authors' conclusions

4.3 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 2015 systematic review.[205] 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 4.1**). Full data extraction tables for included studies are provided in **Appendix A 4.2**.

Figure 4.1 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/

4.3.1 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),[152] France,[208] the Netherlands,[209] Norway,[210] Sweden,[211] Switzerland,[212] and the UK,[213] with two studies conducted for Italy.[214, 215] An overview of general study characteristics and information on the modelling framework for included studies is provided in **Table 4.3**. 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).[213] Five of the nine studies (UK, one for Italy, France, Norway and Switzerland) were industry funded,[208, 210, 212-214] two were funded by government agencies (Alberta, Canada and the Netherlands),[152, 209] one was funded by a research body (Italy),[215] and one declared no funding, but author affiliations included a public health agency and academia (Sweden).[211]

4.3.2 Model characteristics of included studies

Model

Six studies employed a dynamic transmission model to model the impact of varicella vaccination.[208-210, 212-214] The remaining three studies employed an agent-based model,[152] an individual-based model,[215] and a dynamic Markov model.[211] Details of model calibration (and validation in some cases) were described in six of the nine studies.[152, 208, 212-215] Data on social contact patterns for seven studies[152, 208, 209, 211-213, 215] 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.[216] 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),[214] and no detail on social contact patterns was reported in another study.[210]

Table 4.3 General study characteristics of included studies

Study	Year	Country	Model type	Impact of varicella vaccination on herpes zoster incidence included (exogenous boosting)	Time horizon (base case)	Type of economic evaluation	Perspective	Discount rate (costs/health effects)	Funding source
Akpo et al.[213]	2020	UK	Dynamic transmission	Yes	20yrs, 40yrs, 100yrs	CBA; CUA	Healthcare payer; societal	3.5%/3.5%	Industry
Azzari et al.[214]	2020	Italy	Age-structured deterministic dynamic transmission	No	50yrs	CEA	Healthcare payer; societal	3%/3%	Industry
Heininger et al.[212]	2021	Switzerland	Age-structured deterministic dynamic transmission	No	50yrs	CUA	Healthcare payer; societal	3%/3%	Industry
Littlewood et al.[208]	2015	France	Age-structured dynamic transmission	Yes	80yrs	CEA	Healthcare payer; societal	4%/4% until 30yrs after vaccination; 2%/2% thereafter	Industry
Melegaro et al.[215]	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.[210]	2021	Norway	Age-structured deterministic dynamic transmission	Yes (assuned temporary full immunity)	50yrs	CUA	Healthcare payer; societal	3%/3%	Industry
Rafferty et al.[152]	2021	Alberta, Canada	Agent based	Yes	75yrs	CUA	Healthcare payer; societal	1.5%/1.5%	Government
van Lier et al.[209]	2015	the Netherlands	Age-structured dynamic transmission	Yes	up to 180yrs	CEA	Societal	4%/1.5%	Government
Wolff et al.[211]	2021	Sweden	Age-structured dynamic markov	Yes (assumed comparable to live herpes zoster vaccination of limited duration)	85yrs	CUA	Healthcare payer; societal	3%/3%	Independent

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

Time horizon

Studies adopted a time horizon of at least 50 years[210, 212, 214] and up to 85 years,[210] 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.[213, 215]

Perspective

A total of seven studies conducted the analysis from both the payer and societal perspectives,[152, 208, 210-214] while one conducted the analysis from the societal perspective only[209] and one adopted the perspective of the tax-payer.[215]

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,[152, 210-215] ranging from 1.5% for Alberta, Canada[152] to 3.5% for the UK.[213] 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.[209] 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.[208]

Intervention and vaccination strategies

Table 4.4 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[209]
- one study assessed the quadrivalent vaccine for both doses[208]
- in three studies the vaccine type varied between the first and second dose[210, 212, 213]
- 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[214]

- the type of vaccine was not reported in three studies.[152, 211, 215]

Five of the nine studies assessed a strategy with a fixed age at vaccination.[208, 209, 211, 214, 215] Four studies assessed strategies with varying ages at vaccination;[152, 210, 212, 213] three of these four studies specifically assessed both short- and long-dose intervals[152, 210, 212] 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).[213]

Age at first dose ranged from nine months[212] to 15 months,[209, 210, 214, 215] while age at second dose ranged from 12 months[212] to 11 years.[210] 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) [208, 211] and three assessed a long-dose interval of at least three years (Italy [n=2] and the Netherlands).[209, 215] 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),[212] one study varied the first dose by one month maintaining a long dose interval of approximately two and half years for both strategies (UK),[213] and two studies assessed both short- (up to six months) and long-dose intervals (up to 10 years approximately) (Norway and Alberta, Canada).[152, 210]

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)[215] to 95% (Norway, the Netherlands and Sweden).[209-211] 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).[213] 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).[214] 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).[152]

Vaccine characteristics

Estimates of vaccine efficacy/effectiveness used in the included studies varied considerably. Efficacy data were used in five studies,[208, 210, 213-215] effectiveness data were used in three studies,[152, 209, 211] although one study did not report estimates,[152] and one study did not report the type of data or estimate applied.[212] In three of the five studies that used efficacy data, different estimates were used for both one dose and two doses of two different manufacturer's vaccines.[210, 213, 214] For vaccines manufactured by GSK, the efficacy estimate used for one dose varied from 61.7% to 67.3% and efficacy estimates used for two doses varied from 94.6% to 95.4%. For vaccines manufactured by MSD, efficacy estimates used for one dose varied from 78% to 100% and estimates for two doses varied from 97% to 100%. A further study used an efficacy estimate of 80% for one dose and 96% for two doses,[215] while the fifth study reported a single efficacy estimate of 95% for two doses.[208] For the two studies that reported using effectiveness data and supplied data, estimates of 81% and 92%[211] and 90% and 95%[209] were used for one dose and two doses, respectively.

Waning of immunity was considered and waning rates were provided in five studies.[208, 210, 211, 213, 214] Waning rates (absolute reduction) for both one and two doses were provided in all five reviews and varied from 0.02 to 0.06 per annum for one dose and from no waning to 0.013 for two doses. A single review reported separate waning rates for GSK and MSD vaccines.[214] Waning of immunity was not considered in one study [209] and was not reported in three further studies.[152, 212, 215]

Table 4.4 Vaccination strategies and vaccine characteristics considered in the models evaluation routine varicella vaccination

Study	Year	Dosing schedule	Vaccine type	Age at vaccination	Vaccine efficacy/ effectiveness	Waning rate (absolute reduction, per year)	Vaccination coverage
Akpo et al.[213]	2020	2-dose	1st dose mono/quad, 2nd dose quad	1st dose at 13mths (mono), 2nd dose at 3yrs 4mths (quad); 1st dose at 12mths (quad), 2nd dose at 3yrs 4mths (quad)	Efficacy GSK: 1-dose 67.2%, 2-dose 95.4% Efficacy MSD: 1-dose 78%, 2-dose 98.3%	1st dose 0.03, 2nd dose none	1st dose 87%, 2nd dose 87% (mono + quad); 1st dose 95%, 2nd dose 87% (quad + quad)
Azzari et al.[214]	2020	2-dose	1st dose quad, 2nd dose quad; 1st dose mono, 2nd dose quad	1st dose at 13-15mths (mono/quad), 2nd dose at 5-6yrs (quad)	Efficacy GSK: 1-dose 65.4%, 2-dose 94.9% Efficacy MSD: 1-dose 100%, 2-dose 100%	MSD: 1st dose 0.04, 2nd dose 0.013 GSK: 1st dose 0.0588, 2nd dose none	1st dose mono 81%, 1st dose quad 85%, 2nd dose quad 83%
Heininger et al.[212]	2021	2-dose	1st dose quad, 2nd dose mono/quad	1st dose at 9mths (quad), 2nd dose at 12mths (quad); 1st dose at 12mths (quad), 2nd dose at 19mths (quad); 1st dose at 9mths (quad), 2nd dose at 24mths (mono);	NR	NR	1st dose 95%, 2nd dose 90%
Littlewood et al.[208]	2015	2-dose	1st dose quad, 2nd dose quad	1st dose at 12mths; 2nd dose at 18mths	Efficacy: 2-dose 95%	1st dose 0.0588, 2nd dose none	1st dose 90%, 2nd dose 80%
Melegaro et al.[215]	2018	2-dose	NR	1st dose at 15mths; 2nd dose at 5-6yrs	Efficacy: 1-dose 80%, 2-dose 96%	NR	80%
Pawaskar et al.[210]	2021	2-dose	1st dose mono, 2nd dose mono/quad	1st dose at 15mths; 2nd dose at 18mths/7yrs/11yrs	Efficacy GSK: 1-dose 61.7%, 2-dose 94.6% Efficacy MSD: 1-dose: 90.3%, 2-dose 97%	1st dose 0.04, 2nd dose 0.013	95 to 97% (base case value not clear)

Study	Year	Dosing schedule	Vaccine type	Age at vaccination	Vaccine efficacy/ effectiveness	Waning rate (absolute reduction, per year)	Vaccination coverage
Rafferty et al.[152]	2021	2-dose	NR	1st dose at 12mths; 2nd dose at 18mths/4-6yrs	Real world effectiveness (data not reported)	NR	1st dose: Rejectors (3%), Hesitants (75%), Acceptors (97%); 2nd dose: Rejectors (33%), Hesitants (82%), Acceptors (98%)
van Lier et al.[209]	2015	2-dose	1st dose mono, 2nd dose mono	1st dose at 15mths; 2nd dose at 4yrs	Effectiveness: 1-dose 90%, 2-dose 95%	Not considered	95%
Wolff et al.[211]	2021	2-dose	NR	1st dose at 12mths; 2nd dose at 18mths	Effectiveness: 1-dose 81%, 2-dose 92%	1st dose 0.02, 2nd dose none	95%

Key: NR – not reported

4.3.3 Costs - direct and indirect

Direct costs

Across all nine studies, the following direct costs were included in the economic modelling:

- GP visits for varicella and HZ (where included in the model)
- hospitalisation for varicella and HZ (where included in the model)
- vaccine costs.

All studies, with the exception of those for France and Canada,[152, 208] specified that the cost of vaccine administration was included. The studies conducted for Italy[206] and Switzerland[204] specifically included delivery and cold chain costs. Medication, prescription and over-the-counter drugs were included in seven of the nine studies studies,[152, 208, 209, 211, 212, 214, 215] while the cost of diagnostic or additional tests were included in three studies only (Italy, Switzerland and France).[208, 212, 214] Five of the nine studies included direct costs specifically relating to vaccine-related febrile seizures.[152, 208, 212-214] A number of items were included in single studies including the cost of the time required to administer the monovalent vaccine (UK),[213] the programme costs of introducing a new vaccine (e.g., campaign, new leaflets) (the Netherlands),[209] and personal expenses such as travel and gifts (Canada).[152]

Indirect costs

All eight studies that conducted the analysis from the societal perspective included productivity losses for adults ill with varicella and herpes zoster (where included in the model). [144, 199, 200-205] The inclusion of productivity losses for caregivers of those with the disease were specified in six of the eight studies.[152, 208, 209, 211, 212, 214] One study, conducted for France, included the cost of alternative childcare arrangements[208] and a single study, conducted for the Netherlands, included productivity loss due to mortality.[209]

Data required to measure and value costs (both direct and indirect), where reported, are included in the data extraction tables in **Appendix A 4.2**.

4.3.4 Effects - direct and indirect

Direct effects

Across all nine studies, incidence or cases of disease were included in the direct effects of vaccination. Six of the nine studies included the impact on hospitalisations,[152, 208, 210-212, 214] while seven studies included the impact on deaths.[152, 208-210, 212, 214, 215] Outpatient cases were included in two studies (Norway[210] and Sweden[211]), while incidence of complications (France)[208] and vaccine-induced VZV reactivation (the Netherlands)[209] were included in a single study each. Data required to measure and value direct effects, where reported, are included in the data extraction tables in **Appendix A 4.2**.

Indirect effects

Seven of nine studies included and modelled the impact of varicella vaccination on incidence of HZ associated with exogenous boosting.[152, 208-211, 213, 215] 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 HZ.[217] Assumptions with regard to the impact of varicella vaccination on incidence of HZ (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,[213] five years (based on empirical data) in the Canadian study,[152] and 80 years in the study conducted for Norway.[210] The review for Sweden noted that the impact of exogenous boosting was assumed to be comparable to live HZ vaccination with a limited duration of immunity and was modelled as a form of complete immunity to HZ that wanes with time.[211] 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 HZ vaccine.[208]

- Two scenarios were assessed in one of the studies for Italy; temporary complete immunity, where each boosting event provides partial complete immunity to HZ 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.[215]
- 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.[209]

Utility values for quality-adjusted life years (QALYs)

Health state utility values, used to calculate QALYs, were directly reported in three reviews only.[152, 210, 215] The utility values used in these studies were sourced from different studies and varied for the same health states. The health state utility values for varicella ranged from 0.71 to 0.81 for those aged less than 15 years and from 0.62 to 0.74 for those aged 15 years and over. For breakthrough varicella they ranged from 0.81 to 0.92 for those aged less than 15 years and from 0.76 to 0.92 for those aged 15 years and over. A calculated QALY loss per health state was reported in four reviews,[208, 209, 211, 213] with varying detail provided of utility values and duration in the health state used to calculate the QALY loss. The final two reviews reported QALYs per health state[214] and the QALY loss per case associated with each vaccination strategy assessed.[212]

4.3.5 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.[213]
- 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.[215]
- 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 HZ was assumed.[152]
- 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 HZ is assumed and vaccine VZV reactivation is not assumed
    - varicella vaccination is dominated by no vaccination when exogenous boosting of immunity to HZ is assumed and vaccine VZV reactivation is assumed.[209]

4.3.6 Overall study conclusions regarding cost effectiveness

Six of the included studies concluded that two-dose varicella vaccination was cost effective or cost saving,[208, 210-214] including all five of the industry funded studies. Two of the studies noted that the cost effectiveness of varicella vaccination (from the payer's perspective)[152] is dependent on the impact on incidence of HZ associated with exogenous boosting.[152, 209] 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.[215]

4.3.7 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.[207] 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.[209, 212, 215] 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 years.[210, 212, 214] 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 across all studies. Lastly, within the 'Consistency' domain, a number of studies did not describe model validation or consistency checks.[209-211, 214] The full results of the critical appraisal are detailed in Appendix A 4.3.

4.4 Discussion of developments in the methodology for economic modelling of childhood varicella vaccination

4.4.1 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 2015 systematic review (included studies published up until October 2013).[205] Similar to the earlier review, most of the studies in the present review were conducted for European countries, with approximately half of included studies funded by industry.

While 10 of 23 studies in the 2015 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)[211] in the present review were based on dynamic transmission modelling. In the earlier review, most of the models were reported to have ignored the relationship between varicella and herpes zoster, where only four studies modelled the possible impact of routine varicella vaccination on incidence of

herpes zoster. However, seven of the nine studies in the present 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, exposed, infectious, 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.[13, 20, 90] 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.[218]

It has been highlighted 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.[132, 218] While there has been strong support for including the societal perspective, there has been less consideration and consensus as to what it should include.[219] As such, the elements of vaccines that may be undervalued when a payer perspective is adopted, include the prevention of complications beyond the short-term complications directly associated with a particular disease, health gains for care givers, herd effects, community benefits, enhanced productivity and the promotion of equity.[220] Studies included in the 2015 systematic review dated from 1985 to 2013 and those included in the present review dated from 2015 to 2021. Over this timeline of 35 years, the societal perspective has generally been adopted in economic evaluation studies of varicella vaccination. This indicates that the wider benefits of varicella vaccination, beyond those gained solely by individuals that are vaccinated, have long been recognised and included in economic analyses. 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.[130]

Overall, the time horizon adopted in modelling studies in the 2015 systematic review was shorter than that in the present 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 HZ, typically several decades after primary infection, an economic model incorporating a longer time horizon in the base case analysis is arguably the most appropriate.

4.4.2 Intervention and vaccination strategies

Most of the studies in the 2015 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 of vaccination varied more widely in the 2015 systematic review, ranging from 12 to 36 months, compared to a range of nine to 15 months in the present review. This difference may be reflective of underlying differences in the composition of childhood vaccination schedules between individual countries, as well as organisational changes in the timing of the administration in individual countries over time. It may also be reflective of the changing epidemiology of varicella in a particular country or the difference in epidemiology between countries due to different contact patterns. Incidence of varicella infection in those aged up to three years has increased over time in some countries,[221, 222] and seroconversion is

reported to happen sooner in northern and western European countries, compared with southern and eastern European countries.[14] The former may partly relate to increasing numbers of children attending childcare facilities at a younger age in some countries over time, and the latter to both different socialisation patterns for children and different urbanisation patterns between countries.[14] Therefore, changes in the assumptions relating to the age at first dose of vaccination in some modelling studies may reflect the changing epidemiology of varicella infection in the country being assessed or simply different countries being assessed. In the earlier review, assumed vaccination coverage rates (per dose) ranged from 30% to 97%, with the majority of studies assuming a coverage rate between 70% and 90%. Assumed coverage rates were higher in studies in the present 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.

4.4.3 Vaccine characteristics

The efficacy/effectiveness data used for one-dose varicella vaccination strategies varied greatly, ranging from 80 to 97% in the 2015 systematic review, to 61.7 to 100% in the present review. Given the timing of the two reviews, these differences may reflect available data at the time that individual economic modelling studies were conducted. Over time and with an increasing number of countries implementing childhood varicella vaccination programmes, the results of well conducted observational studies of vaccine effectiveness, and not solely RCTs, may be reflected in more recent economic modelling studies. While greater consistency in estimates of vaccine effectiveness might be expected over time, these studies may also be conducted in a wide range of settings, in countries with differing epidemiology, and varying coverage rates, resulting in more uncertainty regarding vaccine effectiveness. These wide-ranging estimates of vaccine effectiveness have the potential to impact on the certainty associated with the overall results of cost effectiveness studies of childhood varicella vaccination.

Approximately 25% of studies in the earlier review did not consider waning of vaccine-induced immunity. Of those that did, almost half used waning estimates of

0.031 per annum for one dose, a number of others used 0.005 and others stated that waning was applied to 15% of those protected by vaccination, without quantifying the estimates applied. A UK study included in the previous review used various waning estimates, ranging from 0.0005 (two dose) to 0.067 (one dose) per annum.[223] Waning of immunity was considered and waning estimates were reported in five of the nine studies in the present review[208, 210, 211, 213, 214] where one dose estimates ranged from 0.02 to 0.0588 per annum. Two of the nine studies assumed waning immunity for two doses, applying the same estimate of 0.013 per annum.[210, 214] Similar to vaccine efficacy/effectiveness data, differing rates may reflect the available data at the time that individual economic modelling studies were conducted.

4.4.4 Costs and effects

Included costs and effects were not detailed in the 2015 systematic review so a comparison with the present review is not possible without de novo review of the underlying studies. However, the earlier review did note that some studies included the cost of vaccine wastage which was not reported as an included cost in the studies in the present review. Overall, the included costs and effects were largely consistent across the nine studies included in the present review; however, the costs associated with vaccine-related febrile seizure were not included in four studies,[209-211, 215] 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, personnel),[209] and two studies did not include the indirect effect of the impact of varicella vaccination on HZ incidence associated with exogenous boosting.[212, 214]

4.4.5 Impact of modelling assumptions on overall results

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 HZ and assumptions around exogenous boosting of immunity to HZ. When no exogenous boosting was assumed, varicella vaccination

was considered to be cost effective. However, the inclusion of the impact on incidence of HZ associated with exogenous boosting 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; the relevant studies did not assess cost effectiveness from the societal perspective. In the present review, while six of the included studies concluded that two-dose varicella vaccination was cost effective or cost saving,[208, 210-214] 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 HZ associated with exogenous boosting.[152, 209, 215] 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 HZ is uncertain,[224-226] modelling the cost effectiveness of varicella vaccination should allow for consideration of this indirect effect.

4.4.6 Strengths and limitations

While routine childhood varicella vaccination has been adopted in a number of countries since the 1990s, there are many countries that do not recommend it. Additionally, where childhood varicella vaccination has been adopted, there is variation in vaccination polices and a number of countries have amended their policies over time. Against both this backdrop and an evolving evidence base on the clinical effectiveness and safety of varicella vaccination, this rapid review adopted a systematic approach to update the available evidence of the approaches taken to the economic modelling of childhood varicella vaccination. In comparing the results of this review to a previously published systematic review, it also provides a comprehensive assessment of the evolution and variability in the economic modelling approaches adopted on this topic over the last 40 years.

There are a number of important limitations to this rapid review. Firstly, the study was conducted by a single reviewer and the search was limited to two databases and a forward citation search of the 2015 systematic review. Secondly, while the critical appraisal did not raise major concerns overall, within some studies there were

aspects of the three quality domains that were poorly reported. As such, important detail with regard to model structure, model input parameters, model validation and consistency checks may not be complete for all included studies. However, given the overall level of consistency in reporting between included studies, this is unlikely to impact the overall results of the review. Lastly, this study included a comparison of a number of original studies with a previously published systematic review. As a direct comparison with the original studies included in the systematic review was not conducted, some of the detail from those studies may have been lost in the comparative analysis.

4.5 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 structural features and input parameter data to be considered in the economic modelling of childhood varicella vaccination. It also highlights developments in the modelling approaches that have occurred over time. Dynamic transmission models are increasingly being used to model the impact of varicella vaccination on VZV transmission and capture the full effects of vaccination, with the epidemiological model output subsequently used in associated economic models. Additionally, and recognising the potential impact of varicella vaccination on the incidence of HZ associated with exogenous boosting, more recent CEAs have typically considered the impact of this indirect effect. Over a considerable period of time, published CEAs of childhood varicella vaccination have typically adopted more than one perspective with analyses conducted from both the payer and societal perspectives and the latter used to capture the full value of vaccination. The findings from this review will be used to inform the development of a de novo economic model of universal childhood varicella vaccination in Ireland.

5 An economic evaluation and incremental analysis of the cost effectiveness of three universal childhood varicella vaccination strategies for Ireland

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5.1 Abstract

Background

The cost effectiveness of childhood varicella vaccination is uncertain, as evidenced by variation in national health policies. Within the European Economic Area (EEA), only 10 of 30 countries offer universally funded childhood varicella vaccination. This study estimates the cost effectiveness of universal childhood varicella vaccination for one EEA country (Ireland), highlighting the difference in cost effectiveness between alternative vaccination strategies.

Methods

An age-structured dynamic transmission model, simulating varicella zoster virus transmission, was developed to analyse the impact of three vaccination strategies; one-dose at 12 months old, two-dose at 12 and 15 months old (short-interval), and two-dose at 12 months and five years old (long-interval). The analysis adopted an 80-year time horizon and considered payer and societal perspectives. Clinical effectiveness was based on cases of varicella and subsequently herpes zoster and post herpetic neuralgia avoided, and outcomes were expressed in quality-adjusted life-years (QALYs). Costs were presented in 2022 Irish Euro and cost effectiveness was interpreted with reference to a willingness-to-pay threshold of €20,000 per QALY gained.

Results

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 QALY gained. The ICER for the next least expensive strategy, two-dose long-interval, compared with one-dose, was estimated at €45,090 per QALY gained. From a societal perspective, all three strategies were cost-saving compared with no vaccination; the two-dose short-interval strategy dominated, yielding the largest cost savings and health benefits. Results were stable across a range of sensitivity and scenario analyses.

Conclusion

A one-dose strategy was highly cost effective from the payer perspective, driven by a reduction in hospitalisations. Two-dose strategies were cost saving from the societal perspective. These results should be considered alongside other factors such as acceptability of a new vaccine within the overall childhood immunisation schedule, programme objectives and budget impact.

5.2 Introduction

Varicella-zoster virus 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 and may reactivate, typically later in life, resulting in herpes zoster. Varicella is very common and highly contagious, mainly affecting children. Approximately 96% of those who are exposed and who do not have acquired immunity, through prior infection or vaccination, will develop varicella, while the lifetime risk of developing herpes zoster is approximately 30%.[8, 68] Annual incidence of varicella in Europe is highest in children under five years of age, ranging from an estimated 7,052 to 16,122 per 100,000 population in Greece and the Netherlands, respectively. Annual incidence in those under five years of age in Ireland is estimated at 11,954 per 100,000 population. Across Europe, seroprevalence of antibodies against varicella in those aged less than 15 years (before the introduction of universal childhood varicella vaccination) is estimated to range from 86.6% in Greece to 100% in Iceland.[27] Seroprevalence 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.[27]

Varicella vaccines are highly effective and are well tolerated.[227, 228] A one dose strategy is highly effective in preventing severe disease and therefore varicella-related hospitalisations. A two dose strategy leads to additional gains in reducing disease transmission and in outbreak control.[227, 229] Significant and sustained reductions in disease incidence and hospitalisations have been achieved in countries that have implemented universal childhood varicella vaccination, including the United States where a programme was introduced in the 1990s.[20, 90, 230] 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%.[13] Similarly, the European Centre for Disease Prevention and Control 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.[20]

In the absence of universal vaccination, the annual incidence of varicella in EU countries typically approximates the annual birth cohort.[20] While varicella is generally a mild self-limiting disease, complications do occur in otherwise healthy children and may include superinfection (usually with Group A streptococcus), skin scarring, and rarely encephalitis, pneumonia, glomerulonephritis, myocarditis, hepatitis and coagulopathy.[37] In Ireland, the total number of births in 2021 was approximately 58,500[231] and it has been estimated that varicella accounts for an average of 1,130 acute hospital and 161 intensive care unit bed days annually.[52] From a societal perpsective, varicella is also associated with substantial productivity losses due to absence from paid work for those caring for children who are ill with the disease. Without universal vaccination, the annual total economic burden (including direct and indirect costs) of varicella across Europe is estimated to be in excess of €600 million, with the total economic burden in Ireland estimated at over €8.5 million.[24] There is a considerable body of published literature of economic evaluations of universal childhood varicella vaccination. A recent systematic review identified 55 studies dating from 1985 to 2022. It reported contrasting conclusions with regard to the cost effectiveness of varicella vaccination programmes, depending on local parameters, dosing schedule, perspective adopted and how the impact on herpes zoster was addressed.[150]

Despite the apparent success of existing programmes, there is ongoing debate about whether vaccination against varicella should be adopted across all countries,[152] and, if recommended, whether a one- or two dose strategy should be implemented. Currently only 10 of 30 countries within the European Economic Area offer funded universal childhood varicella vaccination as part of childhood immunisation programmes.[102] Among the 10 countries, half offer a two-dose short interval programme (where the second dose is typically administered before 24 months of age) and half a two-dose long interval programme (where the second dose is offered after 24 months of age). Outside of Europe, both Australia and New Zealand, amongst others, provide funded one-dose programmes.[98, 232] In Ireland, varicella

vaccination is recommended for certain risk groups only and is not currently included in the routine childhood immunisation schedule.[37]

As policy makers seek to expand childhood vaccination programmes, the demand on budget resources continues to grow. The introduction of a new vaccination programme, with new monovalent and combination vaccines, also presents challenges with respect to the feasibility of including it within the existing immunisation schedule. In economic evaluations of childhood varicella vaccination prorgrammes published to date, no vaccination has typically been the comparator with only a minority of studies undertaking incremental analysis where each potential vacccination strategy was compared with the next least expensive strategy.[150] Additionally, more recent studies for a number countries that did not have a universal programme at the time the referenced economic evaluation was conducted, largely focused on assessing two-dose strategies only, including studies for Norway,[210] the Netherlands,[209] Russia,[233] Sweden,[211] Switzerland, [212] and the UK.[213] Against this backdrop, an assessment of cost effectiveness should include all reasonable potential strategies and thereby seek to identify the most cost-effective strategy to support informed decision-making on the efficient allocation of health resources. In this economic evaluation we compare the cost effectiveness of three varicella vaccination strategies, including both one and two doses, and present a full incremental analysis of the three alternatives.

5.3 Methods

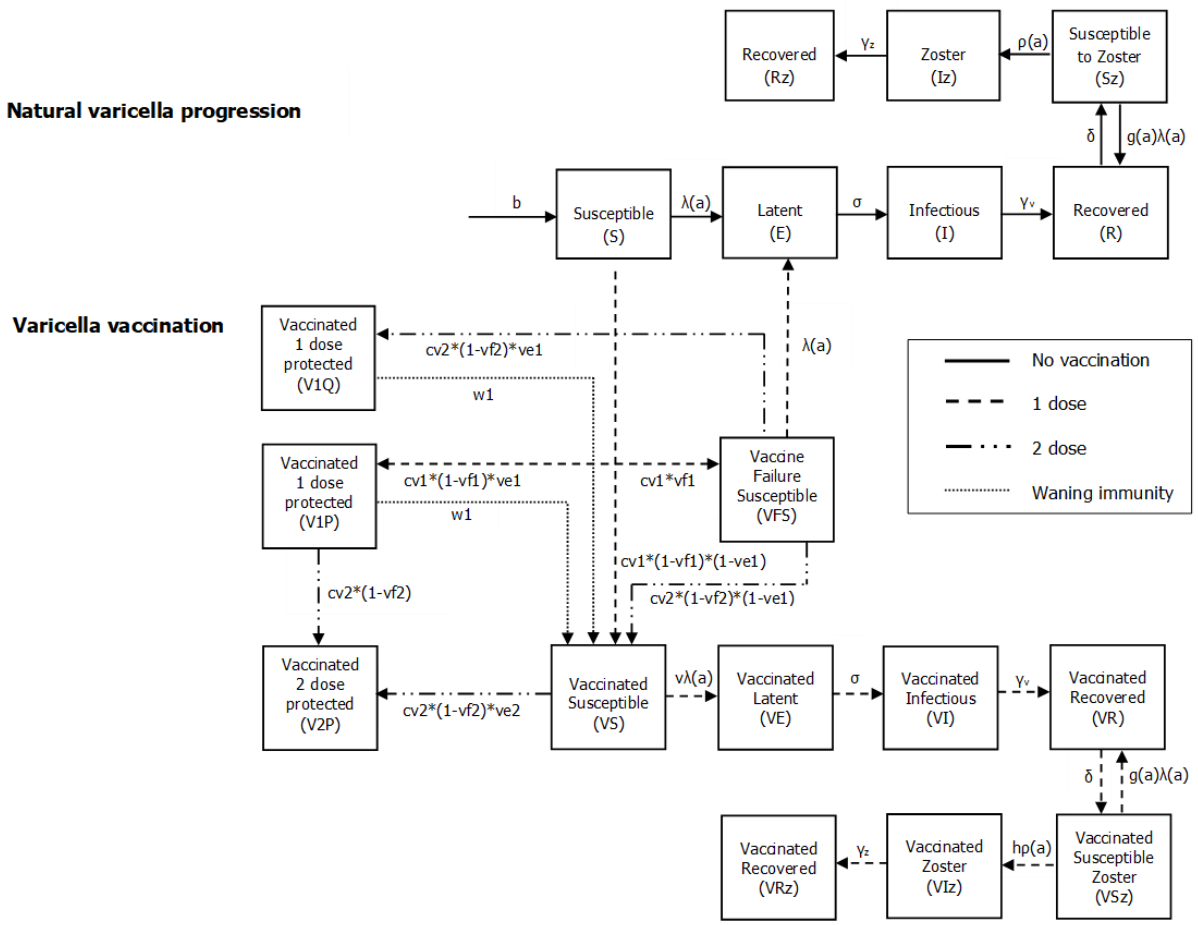
5.3.1 Overview of the Epidemiological and Economic Model Structures

A deterministic, age-structured dynamic model of varicella zoster virus transmission was developed for Ireland using a hypothetical patient cohort. A population of approximately five million people was stratified into 16 age cohorts based on the current population distribution.[231] The model used a system of differential equations to represent the transmission and incidence of varicella and herpes zoster diseases with and without vaccination over an 80 year time horizon. The model was developed in R® (version 4.1.2). A simplified model structure is presented in **Figure**

5.1 illustrating a number of distinct epidemiological states (mutually exclusive compartments) and the movement of individuals (arrows) through the states. The model's estimates of disease incidence were subsequently used in a cost-utility analysis (CUA) that was developed to estimate the costs and health outcomes associated with varicella both with and without vaccination.

The primary objective of the CUA was to estimate incremental cost-effectiveness ratios (ICERs), expressed as the cost per quality-adjusted life-year (QALY) gained. In line with published guidelines for the economic evaluation of health technologies in Ireland, willingness-to-pay thresholds of €20,000 and €45,000 were adopted as reference points for interpreting cost effectiveness.[130] Both payer and societal perspectives were separately adopted, in line with recommended good practice guidelines for the economic evaluation of vaccination programmes.[200] In accordance with national guidelines, costs and outcomes were discounted at a rate of 4%.[130] The CUA was undertaken in Microsoft Office Excel 2013 (Microsoft, Redmond, WA) and R Studio version 4.1.2 (RStudio, PBC, Boston, MA). All data and analyses were reviewed by a second economic modeller [CT]. Model parameters and structural assumptions were reviewed by an expert advisory group comprising clinical, methodological, and patient representatives. Uncertainty was assessed via deterministic and scenario analysis along with a probabilistic analysis that was adapted to deal with the substantial computational overheads associated with dynamic transmission models.

Figure 5.1 Epidemiological model structure



Key: α - ageing rate; b - birth rate; μ - all-cause mortality rate; λ(a) - force of varicella zoster virus infection by age; σ - incubation rate for varicella; γ_v - recovery rate from varicella; δ - waning rate from recovered varicella to susceptible to herpes zoster; g(a)λ(a) - exogenous boosting rate against herpes zoster by age; ρ(a) - reactivation rate of infectious herpes zoster by age; γ_z - recovery rate from herpes zoster; cv1/2 - coverage rate 1-dose/2-dose; vf1/2 - vaccine failure $1^{st}/2^{nd}$ dose; ve1/2 - vaccine effectiveness $1^{st}/2^{nd}$ dose; w1 - waning rate 1-dose; vλ(a) - force of varicella zoster virus infection in those vaccinated by age; h – relative varicella zoster virus reactivation after vaccination.

5.3.2 Modelled vaccination strategies

The target population was all children aged 12 months and the model assumed an annual notional cohort of 55,500 children. Three alternative vaccination strategies were assessed; one dose at 12 months of age, two doses at 12 and 15 months of age (two-dose short interval), and two doses at 12 months and five years of age (two-dose long interval). The timing of administration of the vaccines for both the one-dose and two-dose long interval strategies matches the existing childhood immunisation programme in Ireland. However, the second dose of the two-dose short interval strategy would require an additional healthcare visit for immunisation.

5.3.3 Epidemiological model structure and flows

The epidemiological model was built using Irish demographic data and epidemiological data of varicella and herpes zoster diseases sourced from the Irish Health Protection Surveillance Centre and the academic literature.[16, 27, 231, 234] Age-specific social mixing patterns were not available for Ireland and were therefore estimated from the UK subset of the POLYMOD dataset: this dataset is based on responses to a self-administered paper survey which uses a daily diary to record participants' social contacts.[235] Once individuals entered the model, they followed a pathway of either natural varicella progression or, following the introduction of a vaccination programme, vaccination followed by possible breakthrough varicella. Natural varicella progression comprised four varicella disease states (susceptible, latent, infectious and recovered) with three herpes zoster disease states (susceptible, infected and recovered) following varicella recovery. The flow representing the effect of exogenous boosting, the theory that natural exposure to the varicella virus over the lifespan can inhibit reactivation and subsequent herpes zoster disease, is included in **Figure 5.1**. Exogenous boosting was not included in the base case scenario, but the assumption was investigated in a scenario analysis. While an individual who has herpes zoster can pass VZV to those susceptible to varicella (through direct contact with the fluid from rash blisters), the risk is considered low and therefore was not included in the model.[236] The vaccination followed by

breakthrough varicella pathway comprised four VV 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 included 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 were continuous in the model. A detailed description of the epidemiological model flows and the differential equations for each age group are provided in the supplementary files **Appendix A 5.1** and **Appendix A 5.2**. Epidemiological model input parameters, both biological and vaccine related, are provided in **Table 5.1** and **Table 5.2**, respectively.

5.3.4 Economic model structure

The dynamic transmission model described above estimates the incidence of varicella and herpes zoster disease in a hypothetical population cohort divided into 16 age groups, with and without vaccination. The disease state outputs relating to incidence of disease (numbers infected with varicella and herpes zoster) were subsequently used in the economic model. In the absence of vaccination, it was assumed that those infected with varicella had a non-zero risk of developing severe varicella requiring hospitalisation and those infected with herpes zoster had a non-zero risk of developing severe herpes zoster, requiring hospitalisation, and post herpetic neuralgia. Breakthrough cases in vaccinated individuals were assumed to be non-severe.[229] Non-serious adverse events such as pain, redness and swelling at the injection site and fever and rash were also included as a possible outcome following vaccination.[228] Costs and QALY losses were assigned to each of the health outcomes for both the no vaccination and vaccination scenarios, enabling the calculation of incremental costs and incremental QALYs.

Table 5.1 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 Age group 2: 4.01 Age group 3: 1.33 Age groups 4-6: 1.00 Age groups 7-9: 0.20 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% (assumes a notional birth cohort of 55,500 per year)	CSO[231]
μ	All-cause mortality rate	All-cause mortality rate (by age group)	Age group 1: 0.3244% Age groups 2-6: 0.0056% Age groups 7-8: 0.0051% Age group 9: 0.0230% Age group 10: 0.0430% Age group 11: 0.0867% Age group 12: 0.2102% Age group 13: 0.5283% Age group 14: 1.3808% Age group 15: 4.1994% Age group 16: 13.7546%	CSO[231]
λ(a)	Force of VZV infection	Force of VZV infection (by age group), where λ = β * (I+VI)/N, and β = c*p β = varicella infection rate I = number of infectious people VI = number of infectious people in those vaccinated (breakthrough) 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[235]
		p = the probability of a susceptible person becoming infected with varicella given contact with an infectious person	0.12	Manual calibration to varicella disease incidence data (Appendix A 5.1)
σ	Incubation rate for varicella	Average duration of varicella incubation = 1/σ	14 days	[237]
γ_v	Recovery rate from varicella	Average duration of varicella infection = $1/\gamma_v$	7 days	[237]
δ	Waning rate from recovered varicella to susceptible to HZ	Average duration of cell-mediated immunity following varicella = 1/δ	2 years	[213]
g(a)λ(a)	Exogenous boosting against HZ	Rate of exogenous boosting against HZ (by age group)	100% for all age groups [Explored in a scenario analysis]	Assumption

Parameter	Parameter name	Parameter description	Parameter values		Source
ρ(a)	Reactivation rate of infectious HZ	Reactivation rate of infectious HZ (by age group)	Age group 1: 2.5600% Age group 2: 1.3730% Age group 3: 0.4462% Age group 4: 0.2560% Age group 5: 0.1860% Age group 6: 0.1540% Age group 7: 0.1192% Age group 8: 0.1272%	Age group 9: 0.1292% Age group 10: 0.1501% Age group 11: 0.1772% Age group 12: 0.2379% Age group 13: 0.4869% Age group 14: 0.8417% Age group 15: 1.5616% Age group 16: 3.9661%	Manual calibration to HZ disease incidence data (Appendix A 5.1)
γ_z	Recovery rate from HZ	Average duration of HZ infection = $1/\gamma_z$	7 days		[237]
vλ(a)	Force of VZV infection in those vaccinated	Force of VZV infection to cause breakthrough varicella (by age group)	0.73 * λ(a) [Lower bound 0.5, Upper bound 1.0]		[237]
h	Relative VZV reactivation after vaccination	Reactivation rate of infectious HZ following breakthrough varicella	0.167		[238]

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

Table 5.2 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[239, 240]
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%	-	-	[241]
vf2	Vaccine failure 2nd dose	Probability of complete vaccine failure after 2nd dose	5%	-	-	[241]
ve1	Vaccine efficacy 1st dose	Efficacy of 1st vaccine dose	74%	64%	85%	[227]
ve2	Vaccine efficacy 2nd dose	Efficacy of 2nd vaccine dose (% of individuals unprotected after 1st dose who are protected after 2nd dose)	67% (2-dose VE: 91%)	57% (2-dose VE: 85%)	75% (2-dose VE: 95%)	[227]
w1	Waning rate 1-dose	Waning rate following one dose	4% p.a.	2% p.a.	6% p.a.	[242]

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

Health outcomes

The total number of individuals infected with varicella and herpes zoster (by age group and year) was obtained from the epidemiological model output. The probability of severe disease (requiring hospitalisation) was estimated from the Irish Hospital In-Patient Enquiry system discharge data for years 2015 to 2019 inclusive (**Appendix A 5.3**). These data included the total number of inpatient and day case discharges with a primary diagnosis of B01X Varicella [chickenpox] and 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,[72, 243] with rates consistent with the overall rate assumed in a recent Irish study.[244] 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.[245]

Utility and QALYs

The QALY loss associated with varicella for children was 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), while the QALY loss for varicella for adults was assumed to be the same as that for mild herpes zoster.[246] The average QALY loss associated with herpes zoster and post herpetic neuralgia was sourced from the literature.[247] Base case QALY losses for varicella and herpes zoster disease states are provided in Table 3. The QALY loss associated with mild adverse events following varicella vaccination was excluded in recent economic evaluations, possibly 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 therefore assumed. Based on a utility loss for one day, this equates to an annual utility decrement of 0.0365 which is similar to the base case value used in a previous health technology assessment of human papilloma virus vaccination for boys.[248]

Cost inputs

From the payer perspective, the costs associated with varicella, herpes zoster and post herpetic neuralgia included the opportunity cost of a payer-funded primary care visit (where the cost of the primary care visit is borne by the State and the patient is not required to pay for the visit at the point of care) and the cost of hospitalisation for those with severe disease. Additionally, payer-funded medication costs for treating herpes zoster and post herpetic neuralgia were included. Additional costs under the societal perspective included out of pocket expenses for those required to pay for a primary care consultation and or prescription medication, out of pocket expenses to obtain over the counter medication and the productivity loss of paid work for both those ill and those providing care to individuals sick with varicella, herpes zoster and post herpetic neuralgia and who are unable to attend work. Estimates of direct medical costs and productivity losses used in the analysis are presented in **Table 5.3** and reported in 2022 Irish euro (€). Detailed costing methods

and all economic inputs, including point estimates and ranges for sensitivity analysis are presented in the supplementary file (**Appendix A 5.3** and **Appendix A 5.4**).

Table 5.3 Costs and QALYs

Estimated hospitalisation costs and productivity losses (by age group)				
Age group	Average hospitalisation cost for severe varicella[249, 250]	Average hospitalisation cost for severe herpes zoster[249, 250]	Productivity loss (one day) for carers of those who are ill with varicella, HZ or PHN[251]	Productivity loss (one day) for those who are ill with varicella, HZ or PHN[251]
<1 year	€3,524	€4,598	€143.85	Assumed not of working age.
1 year	€3,827	€4,598	€143.85	
2 years	€4,136	€4,598	€143.85	
3 years	€4,239	€4,598	€143.85	
4 years	€4,192	€4,598	€143.85	
5 to 9 years	€4,057	€4,598	€143.85	
10 to 19 years	€3,797	€5,207	€143.85	
20 to 29 years	€4,451	€5,280	Assumed care not required.	€69.13
30 to 39 years	€4,451	€5,280		€108.08
40 to 49 years	€5,484	€5,064		€155.38
50 to 59 years	€5,484	€5,064		€168.10
60 to 69 years	€7,714	€5,512		€159.95
70 to 79 years	€7,714	€5,344		€119.79
≥80 years	€7,455	€5,236		€119.79
GP and medication costs				
	Varicella (GP visit/medical card patient‡)[252]	Varicella (non-GP visit/ medical card patient‡)[252]	Herpes zoster[244]	PHN[244]
GP visit	€49.72	€54.05	€88.18	€94.23
OTC/prescription medication*	€11.20 to €17.90 (dependent on age) (calculated)		€104.62*	€101.88*
QALY loss†				
	Varicella[246]	Breakthrough varicella[246]	Herpes zoster[247]	PHN[247]
0 to 14 years	0.004	0.001	-	-
≥15 years	0.005		-	-
0 to 69 years	-	-	0.0100	0.1060
≥70 years	-	-	0.0120	0.1560

Note: Detailed costing methods and all economic inputs, including point estimates and ranges for sensitivity analysis are presented in the supplementary file (Appendix A 5.3 and Appendix A 5.4).

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

‡A patient with a GP visit/medical card is not required to pay for the GP visit at the point of care. The cost of the GP visit is borne by the State.

Key: GP – general practitioner; HZ – herpes zoster; OTC – over-the-counter; PHN – post herpetic neuralgia; QALY – quality-adjusted life year.

Vaccination programme costs

For both the payer and societal perspectives, varicella vaccination programme costs included procurement, administration, national cold chain service, (storage and transportation of the vaccines), as well as education and communication about the programme. Vaccine price information was not available, so a vaccine price of €32.73 (excluding value-added/sales tax) was assumed for each of the first and second dose, with no differentiation between the monovalent and quadrivalent measles, mumps, rubella and varicella vaccine. This was calculated as an average of the price of the GlaxoSmithKline monovalent vaccine (£27.31) and the Merck, Sharpe and Dohme monovalent vaccine (£30.30) used in a cost-effectiveness analysis of varicella vaccination for the UK, and using a currency exchange rate of €1/£0.88.[213] The cost for administration of one vaccine dose in the primary care setting was assumed to be €19.73. This was estimated as an average of all contractual payments currently made to primary care practitioners in Ireland under the current national childhood immunisation programmes.[253] 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 was also €19.73. The costs of national cold chain service and education and communication relating to the vaccination programme were assumed to be 3.9% and 1.5% of the vaccine procurement cost respectively, based on historic national immunisation expenditure data.[254]

5.3.5 Sensitivity and scenario analysis

Parameter uncertainty in the economic model 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 variation in single input parameters on the model output are presented in tornado plots. Scenario analyses were conducted to assess assumptions about structural and parameter uncertainties, including the assumption of exogenous boosting, a worst case scenario for vaccine uptake for the two-dose strategies and a number of alternative costs for the vaccine and vaccine administration. In the base-case

scenario, the parameter values for vaccine effectiveness were based on systematic reviews that conducted a meta-analysis (using both randomised controlled trial [RCT] and observational study data) of varicella vaccine effectiveness.[227] A scenario analysis was also conducted where the parameter values for varicella vaccine effectiveness were based solely on the most recent RCT data with 10 years follow-up.[255, 256] Two-dose vaccine effectiveness data in these RCTs were based on a short interval of 42 days between doses.

The robustness of the economic model results was also tested using probabilistic sensitity analysis, wherein 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.

5.4 Results

5.4.1 Base-case analysis

From the payer perspective, all three vaccination strategies were more costly and more effective (fewer QALY losses) relative to no vaccination over an 80 year time horizon (**Table 5.4**). The one-dose strategy produced the lowest average cost-effectiveness ratio per QALY gained (versus no vaccination) of all three strategies (**Table 5.4**). For the incremental analysis, each vaccination strategy was compared with the next least expensive strategy. Relative to no vaccination, a one-dose strategy (vaccination at 12 months of age), had an incremental cost of €37.2 million and a gain of 4,274 QALYs, producing an ICER of €8,712 per QALY gained, versus no

vaccination. A one-dose strategy was therefore considered cost effective at a willingness-to-pay threshold of €20,000 per QALY gained. The two-dose long interval strategy was the next least costly strategy after one-dose. Relative to one-dose, the two-dose long interval strategy (vaccination at 12 months and five years of age had an incremental cost of €51.0 million and a gain of 1,132 QALYs, producing an estimated ICER of €45,090 per QALY gained. The third and most expensive strategy, two-dose short interval (vaccination at 12 and 15 months of age), had an additional cost of €8.7 million and a gain of 233 QALYs, relative to a two-dose long interval programme, producing an estimated ICER of €39,102 per QALY gained. As the principle of extended dominance does not apply in the case of a childhood vaccination programme, where mixed vaccination strategies are not possible, the two-dose long interval strategy could not be removed from our analysis. At a willingness-to-pay threshold of €45,000 per QALY gained, the base case results highlight that the cost effectiveness of the two-dose strategies are highly uncertain from the payer perspective. From the societal perspective, all three vaccination strategies were estimated to dominate no vaccination. When considered from the societal perspective, the estimated total cost savings with vaccination (relative to no vaccination) were €358 million, €379 and €389 million for the one-dose, two-dose long interval, and two-dose short interval strategies, respectively. Overall, the two-dose short interval strategy generated the largest cost savings and largest QALY gains and therefore dominated all other strategies (**Table 5.4**).

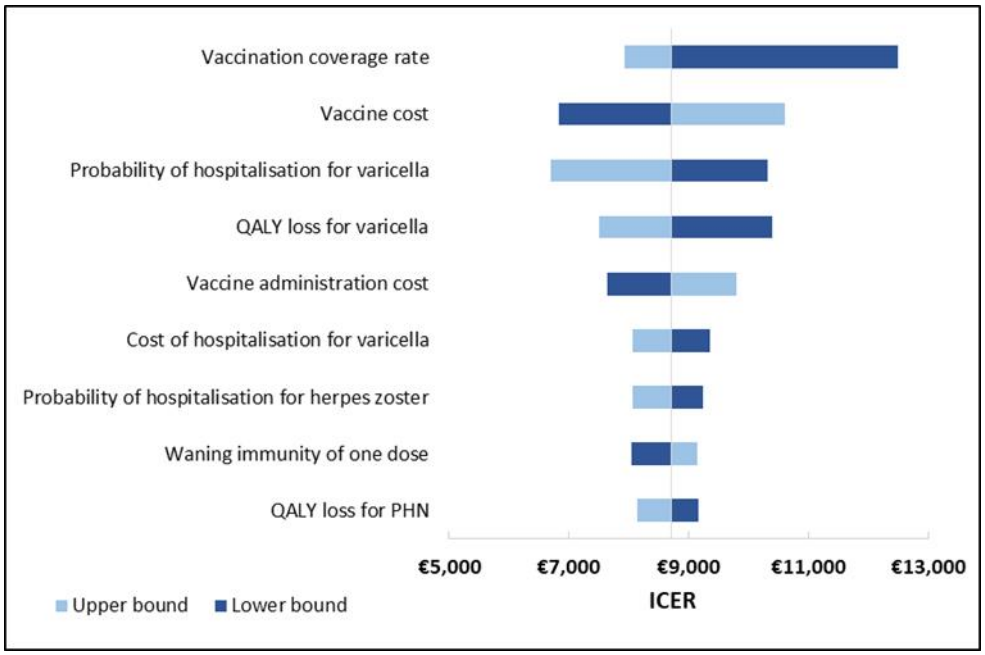
Table 5.4 Cost-utility analysis results

CUA Results	**Payer perspective**							
Vaccination strategy	Total Cost (€, millions)	Total QALYs lost	ACER analysis versus no vaccination			ICER analysis versus previous less costly strategy		
			Incremental cost (€,millions)	Incremental QALYs	ACER/QALY gained	Incremental cost (€,millions)	Incremental QALYs	ICER/QALY gained
No vaccination	€152.8	25,423	-	-	-	25,423	-	
1-dose	€190.0	21,150	€37.2	4,274	€8,712	21,150	4,274	€8,712
2-dose LI	€241.1	20,018	€88.3	5,406	€16,331	20,018	1,132	€45,090[†]
2-dose SI	€249.8	19,795	€97.0	5,629	€17,233	19,795	223	€39,112
CUA Results	**Societal perspective**							
Vaccination strategy	Total Cost (€, millions)	Total QALYs lost	ACER analysis versus no vaccination			ICER analysis versus previous less costly strategy		
			Incremental cost (€,millions)	Incremental QALYs	ACER/QALY gained	Incremental cost (€,millions)	Incremental QALYs	ICER/QALY gained
No vaccination	€859.2	25,423	-	-	Dominated			Dominated
1-dose	€501.2	21,150	-€358.0	4,274	Dominant	-€358.0	4,274	Dominated
2-dose LI	€479.8	20,018	-€379.4	5,406	Dominant	-€21.4	1,132	Dominated
2-dose SI	€470.0	19,795	-€389.2	5,629	Dominant	-€9.8	223	Dominant

5.4.2 One-way sensitivity analysis

The univariate sensitivity analysis demonstrated that the results for the one-dose strategy, relative to no vaccination, were robust to variation of input parameters (**Figure 5.2**). The ICER was most sensitive to a decrease in the coverage rate to 70%, the cost of the vaccine, the probability of hospitalisation for varicella and the QALY loss associated with varicella. However, from the payer perspective, the ICER for the one-dose strategy did not exceed the willingness-to-pay threshold of €20,000 per QALY gained in any of the sensitivity analyses. The ICER for the two-dose long interval strategy, relative to the one-dose strategy, was also most sensitive to a change in the coverage rate. When the coverage rate was reduced to 70%, the ICER increased to €69,000 per QALY gained (**Figure 5.3**). Relative to the two-dose long interval strategy, the univariate sensitivity analysis demonstrated that the ICER for the two-dose short interval strategy, was most sensitive to changes in the waning immunity rate of one dose. This reflects the likelihood of higher waning immunity for the two-dose long interval strategy where the interval between doses is wider (**Figure 5.4**).

Figure 5.2 Tornado plot of univariate sensitivity analysis for a one-dose vaccination strategy versus no vaccination over an 80 year time period[†]



Key: ICER – incremental cost-effectiveness ratio; 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.

Figure 5.3 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†

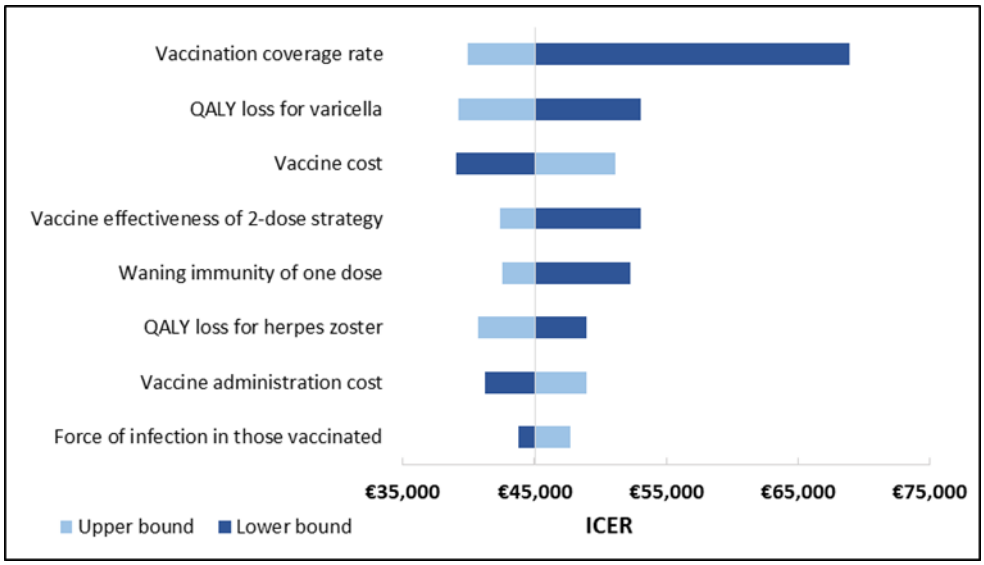
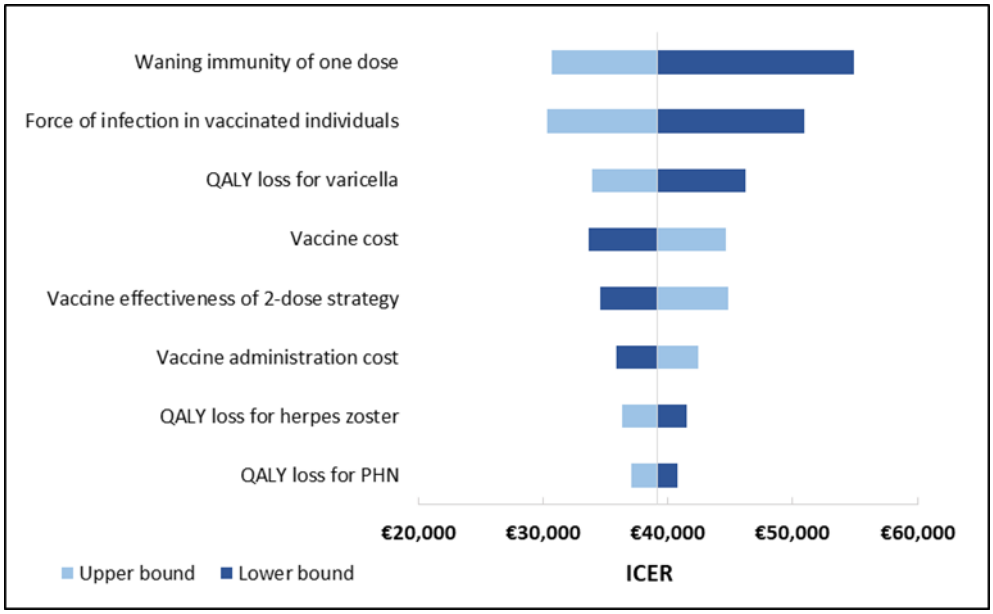


Figure 5.4 Tornado plot of univariate sensitivity analysis for a two-dose short interval vaccination strategy, versus a two-dose long interval strategy, over an 80 year time period†



Key: ICER - incremental cost-effectiveness ratio; QALY – quality-adjusted life year.
†Parameters are ranked in order of decreasing influence on the ICER. Only the most influential parameters are shown.

5.4.3 Scenario analysis

Including an 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 all five age groups from 15 to 59 years for all three vaccination strategies was observed, when compared with no vaccination. In terms of the impact of the assumption of exogenous boosting on cost effectiveness, the one-dose strategy remained cost effective, relative to no vaccination, at a willingness-to-pay threshold of €20,000 per QALY gained. The ICER for the two-dose long interval strategy, relative to the one-dose strategy, was €68,966 per QALY gained, moving it above the €45,000 threshold.

A scenario was modelled to account for lower vaccine uptake than observed in current childhood vaccination programmes in Ireland. 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. The estimated ICER for the two-dose long interval strategy, relative to the one-dose strategy, was €107,000 per QALY gained, exceeding willingness-to-pay thresholds. The complete set of results for the scenario analyses examining assumptions around exogenous boosting, two-dose coverage, vaccine costs and vaccine administration costs are provided in the supplementary file (**Appendix A 5.5**). A final scenario analysis was conducted where vaccine effectiveness data was based on the most recent RCT data with 10 years follow-up.[255, 256] With one-dose vaccine effectiveness set at 74.7%, the estimated ICER for the one-dose strategy, relative to no vaccination, was €8,695 per QALY gained from the payer perspective. With two-dose vaccine effectiveness set at 97.4%, the ICER for the two-dose long interval strategy, compared with one-dose, was estimated at €35,513 per QALY gained and the ICER for the two-dose short interval strategy, versus two-dose long interval, was estimated at €49,321 per QALY gained.

5.4.4 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis demonstrate the robustness of the deterministic cost-effectiveness results of the one-dose vaccination strategy from the payer perspective. The cost-effectiveness plane comparing one-dose vaccination with no vaccination is presented in the supplementary file (**Appendix A 5.6**). From a

payer perspective, 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 willingness-to-pay threshold of €20,000 per QALY gained. The sensitivity analysis 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, the relative positions of both two-dose strategies on the frontier and therefore their associated cost effectiveness at a willingness-to-pay threshold of €45,000 per QALY gained (supplementary file **Appendix A 5.6**). 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 per QALY gained is 47%.

5.5 Discussion

5.5.1 Overview

This CUA modelled the expected clinical and economic outcomes of three universal childhood varicella vaccination strategies for Ireland. From the payer perspective and over an eighty year time horizon, the base case analysis results showed that a one-dose strategy was more costly but saved more QALYs, relative to no vaccination, and was highly cost effective with respect to a willingness-to-pay threshold of €20,000 per QALY gained. The base case findings for a one-dose strategy were supported by sensitivity and scenario analyses. The deterministic ICER for the two-dose long interval strategy, relative to the one-dose strategy, lay close to the willingness-to-pay threshold of €45,000 per QALY gained. As highlighted in the sensitivity analyses, there is uncertainty with regard to the two-dose long interval ICER (driven by a number of parameters including the coverage rate and the vaccine cost) and it is difficult to ascertain, with confidence, if the two-dose long interval strategy is cost effective relative to the one-dose strategy at a willingness-to-pay threshold of €45,000 per QALY gained. The incremental analysis comparing the two-dose short interval strategy (the most costly of the three strategies) to the two-dose long interval strategy (the next least expensive strategy) generated a deterministic ICER

of €39,000 per QALY gained for the two-dose short interval strategy. From the payer perspective, the ICERs for both two-dose strategies were similar and as the probabilistic sensitivity analysis demonstrated, it is not possible to determine with certainty which strategy is more or less cost effective. In the scenario analysis, where vaccine effectiveness data was based on the most recent RCT data only (which found higher vaccine efficacy than the pooled data for a two-dose strategy),[255, 256] the two-dose long interval strategy was cost effective compared to the one-dose strategy at a willingness-to-pay threshold of €45,000 per QALY gained and was more cost effective than the two-dose short interval strategy. Further analysis of the three potential vaccination strategies was conducted from the societal perspective: all three strategies dominated no vaccination with the two-dose short interval strategy the least costly and generating the largest QALY savings. This was mainly due to a reduction in productivity losses as a result of vaccination, with a significant decline in the numbers developing varicella and herpes zoster and therefore a fall in absence from paid work for both those ill and their caregivers.

The univariate sensitvity analysis highlighted that two of the most influential parameters on the ICERs for the one-dose and two-dose long interval strategies were the coverage rate and the vaccine cost. The impact of decreasing coverage rates on cost effectiveness reinforces the advice from the WHO and ECDC regarding the importance and need for sustained high coverage rates for a varicella vaccination programme.[13, 20] If coverage rates are low, the higher risk of breakthrough infection and the reduced benefits of herd immunity undermine the programme as a whole. Furthermore, the results of the scenario analysis highlighted that the cost effectiveness of a two-dose programme, compared with a one-dose programme, is greatly impacted by the coverage rate. If uptake was to fall to 70% for both one and two doses (resulting in 49% population coverage for a two-dose strategy), from the payer perspective the determinsitic ICER for the two-dose long interval strategy, compared with a one-dose strategy, would increase to €107,000 per QALY gained and the strategy would not be considered cost effective.

The uncertainty associated with vaccine cost has a considerable impact on the model particularly given that the base case ICERs for the two-dose strategies lie close to the

willingness-to-pay threshold of €45,000 per QALY gained. In the absence of an indicated varicella vaccine price, the assumed cost of one dose of the vaccine was based on an average of two varicella vaccine prices used in a cost-effectiveness analysis of varicella vaccination in the UK.[213] 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 per QALY gained, compared with no vaccination. However, the ICER for the two-dose long interval strategy, versus the one-dose strategy, rose to €51,121 per QALY gained, becoming increasingly less cost effective relative to the one-dose strategy. Conversely, when the vaccine cost was set at 20% below the base case value, the ICER for the two-dose long interval strategy, versus the one-dose strategy, fell below €40,000 per QALY gained and therefore would potentially be cost effective at a willingness-to-pay threshold of €45,000 per QALY gained. The uncertainty in the cost of the vaccine reflects the confidential nature of price negotiations and agreements between health policy decision makers and vaccine manufacturers. Data relating to vaccine cost are often unavailable to analysts conducting economic evaluations to inform policy decision-making, in advance of a health policy decision on the matter. For this reason, threshold analyses can be important to guide policy makers in such price negotiations.

5.5.2 Comparison with existing literature

The results of our analysis are consistent with results from a recent systematic review of economic evaluations of childhood varicella vaccination programmes, where two-dose strategies were generally less cost effective than one-dose strategies.[150] Similar to our study, at current vaccine prices, varicella vaccination programmes were cost-saving from the societal perspective only. Additionally, and in line with our results, estimates of ICERs were sometimes favourable in relation to local willingness-to-pay thresholds and sometimes not, with results depending on both model inputs and how the model was structured to deal with the effect of vaccination on incidence of herpes zoster. On the issue of the effect of vaccination on incidence of herpes zoster due to reduced exogenous boosting, our results are consistent with results from recent studies from Italy,[214] Norway,[210] Sweden,[211] Switzerland[212] and the

UK[213]. These report that hypothetically reduced exogenous boosting does not compromise the cost effectiveness of the strategies assessed.

Of the 55 studies included in the recent systematic review, 28 assessed a one-dose strategy either alone or in addition to a two-dose strategy. However, only eight of the 28 studies have been published in the past 10 years. More recent studies for countries that did not have a universal childhood vaccination programme at the time the referenced economic evaluation was conducted have largely focused on assessing two-dose strategies only, including studies for Norway,[210] Russia,[233] Switzerland, [212] the UK[213] the Netherlands,[209] and Sweden[211] (the first four of which were industry funded). This apparent shift in the vaccination strategies under consideration may be because a number of countries that initially commenced universal childhood vaccination with one-dose programmes (such as Germany and the USA), subsequently moved to two-dose programmes. However, four of the six studies referenced above were funded by vaccine manufacturers, potentially resulting in bias in the selection of strategies under consideration.[210, 212, 213, 233] Given the effectiveness of a one-dose strategy in reducing severe disease and both the potential difference in budget impact between a one-dose and two-dose strategy and the risk of lower coverage with the latter, arguably a one-dose strategy should be considered as a potential strategy in economic evaluations. Where health budgets are increasingly under pressure due to general increases in healthcare costs and ever more expensive health technologies, all potential strategies should be assessed to establish the efficiency of increasingly costly options. Our study, which included incremental analysis of both one-dose and two-dose vaccination strategies, highlights the cost effectiveness of a one-dose strategy versus no vaccination and the incremental cost effectiveness of two-dose strategies, providing estimates of the efficiency of increasingly costly strategies.

5.5.3 Strengths and limitations

A key strength of our study is the use of a dynamic transmission model. Although a dynamic modelling approach should be employed to model the full range of effects of a varicella vaccination programme, including herd immunity, potential shifts in the

age of infection, waning of vaccine protection, and the impact of vaccination on incidence of herpes zoster due to reduced or absent exogenous boosting, static models continue to be used.[150] Of the 55 studies included in a recent systematic review of childhood varicella vaccination programmes, 21 used a static model; 11 of these were published in the last 10 years.[150] For our CUA, a de novo dynamic transmission model of varicella zoster virus was developed.

A key reason why some countries have not implemented universal childhood varicella vaccination is the potential impact on the incidence of herpes zoster. The use of scenario analysis to examine this effect is a strength of our study. Given that countries that have implemented universal childhood varicella vaccination programmes have not reported a linked rise in incidence of herpes zoster, our base case scenario did not incorporate exogenous boosting.[224, 257] However, we included a scenario analysis which examined the assumption of full temporary exogenous boosting (supplemetary file S5), where the one-dose strategy remained cost effective, relative to no vaccination, at a willingness-to-pay threshold of €20,000 per QALY gained

A further strength is the use of both the payer and societal perspectives. Capturing the full benefits of vaccination in economic evaluations, by adopting a broader perpsective than the payer, is an important consideration.[150, 200, 258] The use of a societal perspective is warranted in the case of varicella vaccination given the considerable productivity losses associated with the disease. In Europe, the indirect cost of varicella has been estimated at over €400 million, accounting for in excess of 65% of the total economic burden of varicella.[24] The uncertainty associated with the results of the cost effectiveness of the two-dose strategies conducted from the payer perspective, also highlights the value of the analysis conducted from the societal perspective. Lastly, our study was conducted by analysts embedded within the Irish healthcare system which facilitated access to input from experts and relevant stakeholders to guide the choice of uncertain base case parameter values. The information asymmetry between analysts embedded in the healthcare system and those in industry noted previously highlights the need for this input.

The present study is subject to a number of limitations. 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. 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.

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 streptococcal (iGAS) infection, 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,[12, 259] 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. 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.[73] 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 probabilistic sensitivity analysis is the preferred approach for exploring uncertainty arising from parameter imprecision,[130] a full analysis of all model input parameters was not possible. Some of the epidemiological model inputs (for example, probability of varicella-zoster virus 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. Similarly, in the case of the univariate sensitivity analysis, it was not possible to vary each model input parameter.

5.5.4 Conclusions

From the payer perspective, one-dose universal childhood varicella vaccination is a cost effective intervention for Ireland. Overall, our results suggest that there is very little difference in cost effectiveness between the two-dose strategies. Any preference for either of the two-dose strategies, may rest with the organisational issues associated with the introduction of a new programme and the feasiblity of implementation against the backdrop of the existing childhood immunisation programme. From a societal perspective both one- and two-dose vaccination strategies are cost-saving. As well as cost-effectiveness results, national policy decisions on the introduction of universal childhood varicella vaccination, and the choice of strategy, will also likely consider a number of other important factors. These include the feasibility of expanding the existing childhoood immunisation schedule, the overall programme objective, that is, whether that the objective is to reduce hospitalisations and complications associated with varicella or to eliminate the disease, and the estimated budget impact of a new programme.

6 Discussion

Varicella (chickenpox) is a common, highly contagious, vaccine-preventable disease that occurs worldwide and mainly affects children. Although typically mild, serious complications requiring hospitalisation occur in less than 1% of cases. One in three people who have had varicella will develop herpes zoster (shingles) during their lifetime. Varicella is also associated with significant productivity loss, mainly due to absence from paid work for those caring for people who are sick with the disease. In Ireland, there are approximately 55,000 cases each year and currently varicella vaccination is not offered as part of the routine childhood immunisation schedule.

The aim of this thesis was to assess the clinical effectiveness and safety of childhood varicella vaccination and the cost effectiveness of universal childhood varicella vaccination in Ireland. The thesis employed evidence synthesis and economic evaluation methods to generate evidence in order to help inform a public health policy decision on including varicella vaccination in the routine childhood immunisation schedule in Ireland.

This chapter firstly summarises the overall results of the thesis and considers the findings in the context of the relevant literature. It then outlines the implications of the findings for public health policy and practice. It reflects on a number of aspects of evidence generation that arose over the course of this work and that are relevant in the context of considerations and opportunities for future research. It summarises the key strengths and limitations of this work and ends with final conclusions.

6.1 Principal findings

Numerous systematic reviews assessing the clinical effectiveness of childhood varicella vaccination have been published over time, albeit they have considered different types of vaccine, different dosage regimens, and different ages at vaccination. As a result, this thesis adopted an overview of reviews approach to assess the totality of the published evidence of the clinical effectiveness of childhood varicella vaccination (Chapter 2). Additionally, the overview of reviews was to used to inform vaccine effectiveness parameter estimates for a cost-utility analysis of universal childhood varicella vaccination in Ireland. From a total of 20 systematic

reviews, published over a 20 year period from 2001 to 2021, there was clear and consistent evidence that vaccination is very effective at reducing varicella and its complications. Estimates of one-dose vaccine effectiveness in preventing varicella from systematic reviews that conducted a meta-analysis varied considerably. Overall, estimates 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, 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.[166] In the single review that conducted a meta-analysis for one-dose effectiveness against moderate or severe varicella, pooled vaccine effectiveness (from observational studies) 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).[165] Estimates of two-dose vaccine effectiveness in preventing varicella, from systematic reviews that conducted a meta-analysis, varied from 87% to 95%. The pooled estimate of vaccine effectiveness of two-dose monovalent varicella vaccine 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).[159] Similarly, 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]).[159] 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).[159] In a single review that conducted a meta-analysis of two-dose versus one-dose vaccine effectiveness, 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).[160]

Overall, the evidence on the effectiveness of varicella vaccination from the overview of reviews suggests that both one- and two-dose strategies are effective in preventing varicella of any severity, with a two-dose strategy demonstrating a higher level of effectiveness. However, both strategies have similar high 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 compared with two doses.

For the same reasons as outlined above for clinical effectiveness, that is, multiple published systematic reviews assessing different varicella vaccination strategies, an overview of reviews was also used to assess the evidence of the safety of varicella vaccination (Chapter 3). Overall, the evidence from 17 systematic reviews, published from 2001 to 2021, 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. These potential harms associated with varicella vaccination must be considered in light of the clinical benefits associated with reduced rates of incidence of varicella disease. 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.

Chapter 4 described a rapid review of the methodology, incorporating model structure and input parameters, of the economic modelling of childhood varicella vaccination. The review combined evidence from a 2015 published systematic review of economic evaluations of varicella vaccination[205] and nine additional studies published since 2013 (to cover beyond the last search date in the systematic review). In addition to identifying relevant model input parameters, the review identified several notable modelling features in economic evaluations of varicella vaccination. Firstly, dynamic transmission models are increasingly being used to accurately model the impact of varicella vaccination on VZV transmission, with the epidemiological model output subsequently used in associated economic models. Secondly, recognising the potential impact of varicella vaccination on the incidence of herpes zoster associated with exogenous boosting, more recent economic evaluations have typically considered the impact of this indirect effect. Lastly, economic evaluations of childhood varicella vaccination are generally conducted from both the payer and societal perspectives, with the latter used to capture the full value of vaccination.

Findings from Chapters 2, 3 and 4 were used to inform the development of and incorporated into an Irish-specific economic evaluation of childhood varicella vaccination, described in Chapter 5. Initially, an age-structured population level dynamic transmission model was developed to analyse VZV transmission in Ireland with and without vaccination. The epidemiological model outputs were subsequently used in a cost-utility analysis (CUA) of childhood varicella vaccination in Ireland. The economic model included a full incremental analysis comparing no vaccination and three alternative varicella vaccination strategies: one-dose (administered at 12 months of age), two-dose short interval (administered at 12 months and 15 months of age), and two-dose long interval (administered at 12 months and five years of age). From the payer perspective, the base case analysis demonstrated that a one-dose strategy was more costly but saved more QALYs, relative to no vaccination, and was highly cost effective with respect to a willingness-to-pay threshold of €20,000 per QALY gained. In the incremental analysis, where strategies were ranked in order of increasing cost and compared with the preceding least costly strategy, the ICERs for both two-dose strategies (two-dose long interval versus one-dose and two-short interval versus two-dose long interval) were similar and lay close to a willingness-to-pay threshold of €45,000 per QALY. As the probabilistic sensitivity analysis demonstrated, it was not possible to determine with certainty which of the two-dose strategies was more or less cost effective. Further analysis of the three potential vaccination strategies was conducted from the societal perspective: all three strategies dominated no vaccination with the two-dose short interval strategy generating the largest cost savings and QALY gains. The difference in the overall result from the societal perspective, compared with the payer perspective, was mainly due to the reduction in productivity losses associated with the intervention. When assessing the impact of varicella vaccination from the societal perspective, varicella vaccination led to a significant reduction in the numbers of people developing varicella and herpes zoster and thereby a decline in absence from paid work for both those ill with the diseases and their caregivers.

Overall, these findings suggest that childhood varicella vaccination is effective and safe and adding it to the routine childhood immunisation schedule in Ireland would be an efficient use of public health resources.

6.2 Interpretation of findings

6.2.1 Clinical effectiveness and safety

As highlighted in Chapter 1, the importance of ongoing surveillance and monitoring of the effectiveness and safety of vaccines is widely recognised by those agencies responsible for authorisation, with processes and systems for monitoring clearly defined.[5-7] As vaccination is a preventive intervention, people are exposed to harm in the form of adverse events when they may not benefit from vaccination, either because they are never exposed to the illness or because the vaccine fails. This means that at the individual level, the benefit-harm balance for vaccination is more heterogeneous than would typically be the case for treatment interventions and so reassurance about vaccine safety is important. Therefore, evidence on the clinical effectiveness and safety of existing vaccines requires updating as new data become available. Additionally, the evolution of vaccination strategies based on existing vaccines (including revisions to the number and timing of recommended doses) and the development of new types of vaccines, necessitate updated evidence reviews on the effects of vaccination.

There are a number of important factors to be considered in the assessment of the evidence of vaccine effectiveness. While RCT data are considered the gold standard for demonstrating vaccine efficacy, observational studies are also important as they help the understanding of vaccine effectiveness in real-world settings. This is particularly the case for vaccines such as those for varicella that have been administered as part of national immunisation programmes for almost three decades. Post-licensure studies help us to understand vaccine effectiveness in settings other than those under RCT conditions and are thus important for establishing ongoing vaccine effectiveness and estimating parameter values for use in studies such as those assessing the cost effectiveness of vaccination programmes.

Capturing and assessing both RCT and observational data on the effectiveness of varicella vaccination was therefore an important part of the research conducted in this chapter. While the consistency of findings across the systematic reviews included in the overview of reviews is important, factors directly impacting vaccine effectiveness such as waning immunity and, in the case of contagious diseases, the vaccination coverage rate also require consideration. There was considerable variability in the estimate of effectiveness of one-dose varicella vaccination against varicella of any severity. However, there was less variability for two-dose strategies, with the evidence clearly suggesting that two-dose strategies are more effective than one-dose strategies in reducing incidence of disease. Estimates of vaccine effectiveness against severe varicella for both one- and two-dose strategies were similarly high.

The evidence of waning immunity, particularly for two-dose strategies, was severely lacking in Chapter 2. It is clear from Chapter 1 (**Table 1.3**) that different countries have adopted different two-dose strategies, with some adopting a short interval and others a long interval. Given that the difference in interval may stretch to a number of years (in Hungary[102] and Luxembourg[96] the interval between doses is as short as three months, while in Latvia[87] the interval is up to six years), the vaccine effectiveness of different two-dose strategies may also differ as immunity wanes following the first dose. Many routine childhood vaccines are intended to provide long-term protection, and therefore follow-up is also required to determine whether vaccine effectiveness is sustained. Gathering data to estimate long-term vaccine effectiveness as part of an RCT can be both challenging and costly. Therefore, such data are often collected using observational studies instead, the findings of which may be at risk of confounding.

In order to successfully control vaccine-preventable diseases, sustained high coverage rates are necessary to achieve high levels of individual protection and sufficient herd immunity levels. Furthermore, the benefits of herd immunity only apply if individuals stay in the herd. Migration between countries with different vaccination policies and coverage rates can therefore impact on the risk of infection. Hence, vaccination coverage rates provide important context for estimates of

vaccine effectiveness and are key parameters in subsequent cost-effectiveness analysis. However, they were generally poorly reported in the systematic reviews included in the overview of reviews.

Of note, only one systematic review, conducted by Cochrane, included in the overviews of reviews of the safety of alternative varicella vaccination strategies was assessed as high quality. Therefore, it is important to provide context to the interpretation of the evidence base and explain how the conclusion of the overview of reviews, that is, that there is clear and consistent evidence that both monovalent and quadrivalent MMRV vaccination are safe, was reached. Firstly, the overview of reviews comprised a substantial evidence base of 34 RCTs and 62 other primary studies/reviews conducted over four decades, with consistent findings that childhood varicella vaccination is safe. Of note, the systematic reviews also included observational studies and case reports from countries with long-established childhood varicella vaccination programmes, such as the USA and Germany. Secondly, the included reviews were published over a 20 year period, during which time the methodology for conducting systematic reviews and guidelines for reporting systematic reviews have evolved and become increasingly formalised. As such, more recent systematic reviews tend to have higher quality ratings when assessed using tools such as AMSTAR 2. Moreover, quality assessment applies to the systematic reviews, and does not imply that the underlying primary studies were of poor quality. It is against this backdrop and in the context of introducing a childhood varicella vaccination programme at this point in time, that it has been interpreted from the evidence base that childhood varicella vaccination is safe.

Given that the USA was the first country globally and Germany was the first European country to implement nationwide routine childhood varicella vaccination programmes, perhaps they are best placed as a basis from which to interpret the findings from the overviews of reviews included in this thesis. Additionally, both countries benefit from having initiated universal childhood varicella vaccination with a one-dose programme and subsequently moved to a two-dose programme. The USA currently has a two-dose long interval programme while Germany has a two-dose short interval programme (**Table 1.3**).

The USA commenced with a one-dose programme in 1995 (recommended for children aged 12 to 18 months) and moved to a two-dose programme in 2007 (second dose recommended for children aged four to six years). Data from three active surveillance areas in California, Texas and Philadelphia demonstrated that there was a substantial reduction (71%, 84% and 79%, respectively) in incidence of varicella within five years of implementation of the one-dose vaccination programme.[260] By year five of the programme, vaccination coverage rates among children aged 19 to 35 months in the three surveillance areas ranged from 73.6% to 83.8%.[260] A study of a USA claims database comprising more than 500 million claim records reported that hospitalisations for varicella, and inpatient and outpatient healthcare expenditures also declined dramatically following the introduction of the one-dose programme.[261] With regard to safety, 10 years of post-licensure surveillance data from the Vaccine Adverse Event Reporting System covering the period from 1995 to 2005, when 48 million doses of the monovalent varicella vaccine were distributed, demonstrated that the vaccine was safe and serious adverse events were rare.[262]

The decline in the number of varicella cases in the USA following the introduction of the one-dose programme plateaued between 2003 and 2006 and outbreaks continued to be reported.[263] As a result, the vaccination policy was revised in 2007 and a two-dose schedule was introduced. By the end of the one-dose programme, incidence of varicella had declined by 90% in the two active surveillance areas that continued to monitor cases, with vaccine coverage among children aged 19 to 35 months reaching between 92% and 94%.[264, 265] Data from both active and passive surveillance systems reported additional declines in incidence of varicella in the early years of the two-dose programme and onwards through to 2019. Based on continuous passive surveillance in four areas, a >97% decline in incidence was reported over the 25 years of the programme from inception to 2019, with the largest declines reported in those age groups most likely to have received the second dose.[264] Published data for the 2021-2022 school year reports coverage rates for varicella vaccination among children in kindergarten in the USA of 92.8%.[266] Given the high coverage rates that have been achieved, those individuals who were not

vaccinated in the early years of the programme in the USA and did not have varicella as a child, have likely received the benefits of herd immunity while they remain within the USA. However, if they travel as adults, particularly to countries where VZV circulates widely, they are at risk of infection and as adults are at greater risk of complications. During the period from 2006 to 2020, approximately 132.8 million monovalent and 35.5 million quadrivalent MMRV vaccines (introduced in 2005) were distributed in the USA. An analysis of passive surveillance data by vaccine type, recorded in the USA Vaccine Adverse Event Reporting System for this period, reported that there were no new or unexpected adverse events, thereby reinforcing the favourable safety profiles of both varicella vaccines.[267]

Germany commenced with a one-dose universal varicella vaccination programme in 2004 (recommended for children aged 11 to 14 months) and moved to a two-dose programme (second dose recommended for children aged 15 to 23 months) in 2009. In 2005, a country-wide varicella sentinel surveillance system was implemented by the Robert Koch Institute to monitor disease incidence and vaccine uptake and to evaluate the vaccination programme. Data were collected from the beginning of 2005 to the end of 2017.[268] Between April 2005 and March 2009, when one-dose was recommended, a 55% reduction in varicella cases in all age groups was reported with a 63% reduction in the age group up to and including four years.[89] Between 2006 and 2017, which incorporated the change in recommendation to a two-dose strategy, a 90% reduction in varicella cases in all age groups was reported with a 95.5% reduction in the age group up to and including four years.[268] The decline in incidence of varicella in Germany was most pronounced during the first 10 years after the introduction of childhood varicella vaccination, possibly explained by the increasing uptake rates over that time. Coverage rates among school-children for the first dose were less than 50% in 2009, rising to over 80% by 2014, with only a moderate increase since then.[268] In the three years after the introduction of the one-dose programme, the largest declines in the annual number of hospitalised varicella cases were reported in the one to four year old age group (from >20 hospitalised varicella cases per 100,000 population in 1994-2004 to 10 in 2007) and in infants (>30 in 1994-2004 to 21 in 2007).[89]

The findings from the overviews of reviews are consistent with the surveillance data available from both the USA and Germany. A one-dose strategy has been effective in reducing incidence of varicella disease, including hospitalisation, in both countries. However, estimates of the reduction in incidence of varicella under a one-dose strategy vary considerably between the two countries. A significantly greater reduction in incidence (>90%) has been observed in both countries following the change to a two-dose strategy. This has been achieved in both countries with coverage rates of at least 80%, meeting the varicella vaccination coverage target set by the WHO.[13] In the USA, the largest declines in incidence over the 25 years of the programme were reported in those age groups most likely to have received the second dose, suggesting that a two-dose strategy does provide long-term immunity against varicella. The findings relating to the safety profile of varicella vaccines are also consistent with the USA surveillance data that covers a 15 year period during which approximately 168 million varicella vaccines (both monovalent and quadrivalent) were distributed.

A number of aspects of the evidence relating to the effectiveness of childhood varicella vaccination in the USA and Germany warrant further consideration. Given that both countries commenced their childhood varicella vaccination programmes with a one-dose regimen and subsequently moved to a two-dose strategy, it's important to understand the rationale behind these decisions. The strategies likely reflect the timeline of RCTs examining the efficacy of the varicella vaccine in young children. The first trials were conducted in the 1980s and early 1990s and they assessed one dose only.[269, 270] The protective efficacy of one dose of varicella vaccine in children was estimated at between 72% and 98% in these trials, the results of which likely informed varicella vaccination policy, and the decision to implement a one-dose programme in those countries who were early adopters. In the USA specifically, post licensure monitoring demonstrated that while one dose was highly effective in reducing severe cases of varicella, it was not enough to provide herd immunity and interrupt virus transmission. Outbreaks continued to be reported, particularly in settings with high contact rates including schools.[263] The results of subsequent RCTs, published in the 2000s, reported significantly higher efficacy for

two doses compared with one dose.[271] The evidence was thus available from the mid-2000s to support the introduction of a two-dose strategy to help improve control of varicella, over and above what had been achieved with one dose. If one dose was demonstrated to be highly effective in reducing severe disease, one may ask why it was necessary to move to a two-dose regimen. Vaccines are the most effective way to prevent many infectious diseases and childhood immunisation is a cornerstone of the public health system in many countries to protect children. Given the experiences in the USA and Germany, where outbreaks continued to occur under a one-dose strategy and vaccinated individuals developed varicella, arguably a one-dose regimen has the potential to undermine the vaccination programme in question and indeed the entire childhood vaccination programme. Parents could reasonably question the benefits of vaccination if their vaccinated child still develops a particular disease. In addition to budgetary considerations, a decision in any country 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. However, the wider consequences of a decision to opt for a one-dose strategy should be thoroughly assessed.

With respect to the difference reported in one-dose vaccine effectiveness between the USA and Germany, this can possibly be explained by different social contact patterns between countries. As outlined in Chapter 1, within Europe alone there is evidence of differences in the age of seroconversion for VZV antibodies, where it occurs earlier in Northern and Western Europe, compared with Eastern and Southern Europe.[14-16] It has been argued that these differences may relate to both earlier socialisation in the community in some countries, where greater numbers of children attend childcare facilities at a younger age, and different urbanisation patterns between countries.[14] Thus where vaccine effectiveness is not sufficiently high to offer immunity to all of those vaccinated and outbreaks occur in particular settings, retrospective estimates of vaccine effectiveness may differ depending on the contact rate levels within those settings.

The findings on the safety of varicella vaccination specifically relating to local and systemic reactions, can be considered further within the context of vaccine reactogenicity. Reactogenicity is a physical manifestation of the inflammatory response to vaccination and includes short-term adverse events, that is local and systemic reactions, that occur shortly after vaccination. Vaccine reactogenicity is assessed as vaccines are developed as well as during clinical trials for establishing the safety of vaccines, where information on these side effects of vaccination is actively sought. A number of factors that can influence reactogenicity have been identified, including host characteristics, such as age, gender, general health and pre-existing immunity, as well as vaccine administration and vaccine composition.[272] With respect to childhood varicella vaccines specifically, in the absence of observed evidence it is plausible that both age and vaccine composition may impact on reactogenicity. Changes in the physiological functions of the immune and nervous systems that occur as people age, can influence susceptibility to adverse reactions to vaccination. It is reported that babies and young children typically display fewer local reactions after vaccination compared with adults, but are more likely to experience fever due to vaccination or other infections at the time of vaccination.[272] Varicella vaccines are live-attenuated vaccines composed of a host of antigens and immune triggers. This potentially makes them more reactogenic than other non-live vaccines.[272] While all vaccines have some risk of adverse events, the findings from Chapter 3 suggest that local and systemic reactions following varicella vaccination are common but generally mild and therefore don't impact considerably on the individual vaccinated. However, the causes of reactogenicity and the reasons for varying levels between different vaccines are largely unknown meaning more research is required to inform the design of less reactogenic vaccines.[272]

6.2.2 Economic modelling and cost effectiveness

The critical choice in infectious disease modelling conducted as part of an economic evaluation of vaccination is that between a static or dynamic model.[132] Based on the findings from Chapter 4, a dynamic transmission model of VZV was developed as part of the economic evaluation of childhood varicella vaccination conducted for Ireland. A recent systematic review of economic evaluations of varicella vaccination

programmes highlights the need for a dynamic transmission model to accurately model the impact of varicella vaccination.[150] These findings are also in line with guidance from the WHO that helps to determine when dynamic or static models are appropriate when vaccination is being considered against infectious disease in humans.[132] In the case of childhood varicella vaccination, a dynamic transmission model is always preferred as varicella is an infectious disease where human to human transmission is common and the eligible target group for vaccination (that is, young children) is an epidemiologically influential subgroup.[132]

As outlined in Chapter 1 (Section 1.6.3), a key assumption in many decision analytical models is that the individuals being modelled are independent of each other with respect to their health and interaction between individuals is not considered to be of importance. However, in the case of communicable infectious diseases, including varicella, the risk of an individual contracting the disease is dependent on the force of infection which in turn is partly dependent on the number of infectious individuals in the population at a given time and the level of contact with these individuals. As such, the communicable nature of an infectious disease impacts the effectiveness of an intervention and decision analytic models developed to assess the cost effectiveness of interventions may need to account for these features. Dynamic transmission models specifically enable the interaction of individuals to be captured and therefore allow for a changing force of infection over time.[129, 135]

Dynamic transmission models also enable the outcomes of vaccination beyond those that accrue to the vaccinated individual to be modelled and therefore appropriately assessed in an economic evaluation. In terms of positive externalities, maintaining sufficiently high coverage rates for a vaccine such as varicella can lead to population-level effects including herd immunity, where those who may be unable to receive the vaccine are protected. Conversely, the introduction of an intervention such as vaccination also has the potential to shift the age profile of unvaccinated people developing the disease. This could potentially lead to more severe disease, due to the higher risk of varicella-related complications with increasing age, and therefore higher costs accruing to both individuals and the health system, impacting on the cost effectiveness of vaccination. Arguably, ignoring these externalities in an

economic evaluation could lead to unsound conclusions and potential be misleading when used to inform public health policy. A number of studies have assessed the impact of vaccination on the epidemiology of varicella. Studies in both the USA and Germany, conducted over periods of between 15 and 20 years, reported no evidence of a significant shift in the burden of varicella to older age groups.[268, 273, 274] Within the modelling study conducted as part of this thesis, the average annual number of varicella cases over a 15 year period similarly showed no significant evidence of a shift in the burden of varicella to older age groups. Declining incidence was observed across childhood and adulthood for all three vaccination strategies, with the exception of an increase in incidence in the age groups from 15 to 49 years for the one-dose strategy. The potential for a shift in disease incidence to older age groups, particularly those beyond childhood, highlights the need for robust ongoing disease surveillance.

One of the unique features of VZV is that it potentially leads to two different diseases, varicella typically in childhood and herpes zoster typically several decades later in adulthood. When modelling the potential impact of varicella vaccination on incidence of herpes zoster associated with exogenous boosting, the rate of exogenous boosting is a function of the force of VZV infection. Given that a dynamic transmission model enables a changing force of infection over time, it allows for the impact of varicella vaccination on incidence of herpes zoster associated with exogenous boosting to be modelled more accurately than would be the case with a static model which doesn't allow for a changing force of infection over time.

While dynamic transmission models may be preferred for modelling the impact of childhood varicella vaccination, there are challenges associated with developing and operationalising them. Dynamic transmission models are analytically more complex than static models and typically require more time and effort to develop and more computer power to implement. Economic evaluations, regardless of the underlying type of decision-analytic model, typically require a considerable number of inputs that may be supported by weak data. However, dynamic transmission models are arguably more data hungry than static models, driven by more intricate and flexible modelling of disease and intervention pathways. Despite the challenges associated

with building and operationalising dynamic transmission models, the evidence, as reported in Chapter 4, suggests that such models are increasingly been used in the economic modelling of childhood varicella vaccination.

Based on the findings from Chapter 4, this economic evaluation was conducted from both the payer and societal perspectives. 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.[132, 218] This model feature is also highlighted in the findings from a systematic review of economic evaluations of varicella vaccination programmes published in 2023.[150] The systematic review reports that the majority of included studies were conducted from both the payer and societal perspectives. Crucially, the review also emphasises the importance that the perspective adopted can have in the public health decision to adopt a vaccination programme or not, as incremental cost-effectiveness ratios can differ markedly depending on the perspective of the analysis.

The results of the CUA conducted as part of this thesis are consistent with the overall results from the same systematic review identified above. From the payer perspective, two-dose strategies are generally less cost effective than one-dose strategies, when compared with no vaccination.[150] As demonstrated in Chapter 5, the ICERs for one-dose versus no vaccination and two-dose versus one-dose are particularly sensitive to both the cost of the vaccine and the vaccination coverage rate (due to the contagious nature of varicella). The vaccine cost is often the subject of confidential pricing agreements between individual countries and vaccine manufacturers. It is often unknown until after such time that a policy decision is made to offer vaccination, and therefore the uncertainty in the results due to this parameter is expected. With respect to vaccine coverage rates, they are subject to variation both between countries and within countries over time. Within individual countries, and as highlighted for Ireland in Chapter 1, coverage rates can differ between different vaccines, depending on the age at which the vaccine is offered and the timing of administration within the overall immunisation schedule. Additionally, the impact of different vaccine coverage rates will depend on each country's local epidemiology of VZV. Thus the uncertainty in the economic evaluation results, due

to assumptions made regarding the vaccine coverage rate is also anticipated. Of note, the ICER for a two-dose long interval strategy compared with a one-dose strategy was higher when coverage rates were lowered in the sensitivity analysis. With lower coverage, one would expect more circulating virus and therefore that the second dose may provide increased protection leading to a lower ICER. However, the two-dose long interval strategy is subject to a waning period of four years after the first dose. With more circulating virus in a low coverage scenario, the two-dose long interval strategy may thus be less effective and therefore less cost effective (when compared with a one-dose strategy) than the same strategy in a high coverage scenario.

Given that the CUA findings are consistent with those from a previously published systematic review, one may legitimately question why a de novo CUA was required for Ireland. There are a multitude of reasons why the cost effectiveness of health technologies may differ between locations and jurisdictions.[(275)] These reasons include differences in the incidence and severity of disease, in the organisation and availability of health care resources, in the unit costs of resources required to deliver health care and in the unit costs of health technologies.[(276)] The extent of variation in estimates of the cost effectiveness of pharmaceuticals has been demonstrated in a review conducted for European countries, where differences in cost effectiveness results between countries were found not to be systematic, resulting in difficulty in making inferences from one country to another.[(277)] The EU Regulation (Regulation (EU) 2021/2282) on health technology assessment (HTAR) that will apply from 12 January 2025 provides for mandatory European cooperation on joint clinical assessments for HTAs of new health technologies including medicines and high-risk medical devices.[(278)] Of note, the regulation focuses on the 'clinical domain' of HTA, as in principle this is the component that is more generalisable from setting to setting. The 'non-clinical domain' of HTA, which includes the assessment of cost effectiveness, will remain the responsibility of individual member states.[(279)]

Assessing the published literature by publication date suggests that there has been a change in the nature of varicella vaccination strategies under consideration in cost-effectiveness analyses. While older studies assessed the cost effectiveness of one-

dose vaccination only, more recently published studies have largely focused on assessing two-dose strategies only, without consideration of a one-dose strategy. This is despite the fact that the evidence suggests that both one- and two-dose strategies are similarly highly effective in preventing severe disease. Of note, many of the recently published studies that only compared two-dose vaccination with no vaccination were funded by vaccine manufacturers,[210, 212, 213, 233] potentially resulting in bias in the selection of strategies under consideration. Health budgets are increasingly under pressure due to general increases in healthcare costs and ever more expensive and an increasing number of health technologies to fund. Against this backdrop, all potential vaccination strategies should be assessed to establish the efficiency of increasingly costly options. In omitting potential strategies from the economic analysis, the cost effectiveness of those strategies considered may be potentially misleading. Additionally, from a budget impact perspective solely, the cost of vaccine procurement and administration for a two-dose strategy is likely to be up to double that of a one-dose strategy. For some countries, a two-dose strategy may simply be unaffordable. If a one-dose strategy is assessed for cost effectiveness, the impact on incidence of herpes zoster should be included in the analysis as, based on the review of clinical effectiveness, a one-dose strategy may leave a larger portion of the population susceptible to herpes zoster later in life. Excluding it from the analysis may bias the results in favour of a one-dose strategy.

6.3 Implications for public health policy and practice in Ireland

To help inform decision-making regarding the potential addition of varicella vaccination to the childhood immunisation schedule in Ireland, this thesis involved:

- a synthesis of the international evidence on the effectiveness and safety of varicella vaccination
- the development of a dynamic transmission model of VZV and a de novo economic evaluation of universal childhood varicella vaccination in Ireland.

The findings from Chapters 2, 3 and 5 provide very strong evidence that childhood varicella vaccination is effective and safe, and depending on the vaccination strategy

and perspective of the analysis, universal childhood varicella vaccination would be cost effective or cost saving in Ireland. However, the findings from these chapters alone cannot fully inform a public health policy decision regarding the addition of varicella vaccination to the childhood immunisation schedule. As outlined in Chapter 1 and set out by the WHO (**Figure 1.3**), there are a number of other factors that require consideration in informing a public health policy decision on adding a vaccine to an immunisation schedule. These include organisational, social, affordability and ethical issues among others.

6.3.1 Organisational considerations

From an organisational perspective, adding a new vaccine to the childhood immunisation schedule in Ireland would have resource implications for both general practice and the school-based immunisation programme (in the event that a two-dose long interval strategy was chosen and the second dose was administered at five years of age). The potential impact on current practice and the extent to which additional resources would be required would likely depend on a number of factors, including the dosage strategy, the timing of the vaccine doses with regard to the existing schedule and the type of vaccine, that is, the monovalent varicella only or quadrivalent MMRV vaccine. Each of the three possible varicella vaccination strategies would likely give rise to different organisational implications as follows:

- A one-dose strategy, with the vaccine administered at 12 months of age, would align with the existing childhood immunisation schedule (**Table 1.4**) where the MMR and Meningococcal B vaccines are also administered at 12 months. However, adding a third vaccine to the schedule may prolong this vaccination visit, potentially impacting on capacity in primary care.

- A two-dose short interval strategy, with the vaccine administered at both 12 and 15 months of age, would align with the existing immunisation schedule for the first dose, as described above. Currently, there is no scheduled vaccination visit at 15 months of age, so this strategy would require the addition of a new GP vaccination visit. This strategy would therefore place an

additional burden on primary care, over and above that for a one-dose strategy, and would have an impact on GP resources.

- A two-dose long interval strategy, with the vaccine administered at both 12 months and five years of age, would also align with the existing childhood immunisation schedule for the first dose, as described above. Additionally, it would align with the current school-based immunisation programme for the second dose, as the 4 in 1 vaccine to protect against diphtheria, polio, tetanus and whopping cough and the MMR vaccine are administered in Junior Infants (at four or five years of age). Therefore, the two-dose long interval strategy may result in additional time required for existing vaccination visits.

The potential organisational impact of adding varicella vaccination to the childhood immunisation schedule should therefore be considered separately for each potential vaccination strategy.

6.3.2 Acceptability of a new vaccine

The potential acceptability of a new vaccine should also be a key consideration in a health policy decision to offer the varicella vaccine to children. While varicella can result in complications and death, these events are extremely rare (Chapter 1). Given the widespread incidence of varicella in young children in temperate countries where vaccination is not offered, it may be seen as an inevitable disease for them, where they typically develop manageable symptoms and acquire lifelong immunity. This view may also reflect a lack of knowledge regarding the link between varicella and herpes zoster, and possibly the fact that most parents of young children have not directly experienced herpes zoster at the age when they are making choices about vaccinating their children. If varicella is generally viewed as an inevitable disease, adding varicella vaccination to the childhood immunisation schedule may have implications for uptake of a new vaccine. A study from the Netherlands reports that a majority of parents and public health professionals have a negative attitude or low intention to vaccinate universally against varicella, due to the perceived low severity of the disease.[280] Additionally, this view of varicella could potentially lead to a

perception that the overall immunisation schedule is unimportant, thereby impacting adherence to and undermining the existing programme.[281] In this context, consideration should also be given to whether the choice of a two-dose long-interval strategy could create issues with uptake for both the varicella and MMR vaccines, either if the varicella vaccine is provided as a quadrivalent (MMRV) vaccine or if a second injection is required (that is, an MMR vaccine and a separate monovalent varicella vaccine). If uptake of the varicella vaccine specifically is low, it could result in reduced uptake of the MMR vaccine where the combined MMRV vaccine is offered. However, in the absence of any evidence, it could also be argued that if a varicella vaccine had high acceptability, it may increase uptake of the MMR vaccine.

As new vaccines are added to the childhood immunisation schedule, the total number of vaccines offered may also impact the acceptability of a new vaccine. It has been argued that parents may fear that multiple vaccines 'overload' a child's immune system even though there is no scientific basis for this view.[282] Some argue that there is a limit to the number of included vaccines in a national immunisation programme, after which the legitimacy of the programme as a whole is undermined.[283] 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 both countries, 'complications following vaccination' and 'too many vaccinations'.[284] A UK study published in 2023 found that although parents have a preference for their child to have fewer injections, a majority of parents would accept a varicella vaccine even if it required an additional injection.[285] Thus policy makers should have legitimate concerns about the acceptability of a new vaccine offered as part of the childhood immunisation schedule both if the disease is perceived as non-serious and if it adds to the total number of vaccines offered.

Uptake of some recommended childhood immunisations in Ireland are currently below WHO targets, with concerns about safety and vaccine side effects reported as the most common reason for missed vaccines.[111] The key sources of vaccination information identified by parents in Ireland are GPs, practice nurses and vaccination information materials published by the Health Service Executive (HSE).[111] Therefore,

an information campaign for parents focusing on the safety of the varicella vaccine, and delivered through the sources identified above, would be an important consideration in the context of adding the vaccine to the childhood immunisation schedule.

As outlined in Chapter 1 (section 1.5.1), the lowest reported coverage rates (between 80% and 85%) for childhood vaccines in Ireland at 24 months of age, are for the full recommended number of doses of vaccine against haemophilus influenzae type b, meningococcal C disease and pneumococcal disease.[104] The final recommended dose of each of these three vaccines is administered at 13 months of age, one month following the most recent vaccination visit. This is the shortest interval between vaccines in the childhood immunisation schedule (**Table 1.4**). Arguably, the scheduling of this visit so soon after the last, may place a burden on some parents or guardians. With respect to the vaccination strategies assessed for varicella, this is a particular issue with the two-dose short interval strategy where the second dose would be administered at 15 months of age and require a new vaccination visit. Therefore the positioning of a new vaccine within the existing immunisation schedule should be a key consideration in a decision to expand the programme.

6.3.3 Affordability and equity

Although this research assessed the subject of efficiency and value for money associated with universal childhood varicella vaccination in Ireland, it did not assess the issue of affordability. Regardless of value for money, the upfront costs and the ongoing annual cost of a vaccination programme may not be affordable for the public health purse. A budget impact analysis would therefore be an important consideration in a public health policy decision. It would enable an assessment of both the direct costs associated with adding varicella vaccination to the childhood immunisation schedule and the savings resulting from the introduction of the intervention. These estimates would then be combined to establish the incremental budget impact of a universal childhood varicella vaccination programme in Ireland.

Currently, the monovalent varicella vaccine is marketed in Ireland and is available for those who wish to purchase it privately and have their children vaccinated. However, the vaccine is not affordable for all and therefore there is a financial barrier to accessing it. Additionally, anecdotal evidence suggests that not everyone is aware that there is a vaccine available that protects against varicella. The addition of the varicella vaccine to the childhood immunisation schedule in Ireland would therefore remove the inequity of access due to the financial barrier and ensure that the vaccine is available, free at the point of care, to all of those eligible to receive it.

6.3.4 Monitoring of varicella burden

A number of international studies conducted since the COVID-19 pandemic provide evidence that the introduction of various non-pharmaceutical interventions to prevent SARS-CoV-2 transmission, impacted typical transmission of other communicable diseases including varicella. Incidence rates of varicella dropped significantly during the pandemic, with increased occurrence observed following the removal of interventions.[286-289] In some countries without universal childhood varicella vaccination programmes, the epidemiology of varicella is reported to have changed post-pandemic. In France, it is reported that children with varicella were slightly older in 2021 than they were during the pre-pandemic period of 2018 to 2019.[288] In England, the age profile of the disease is also reported to have shifted since the pandemic. Incidence rates of varicella among the age groups less than 12 months and between one and four years are more similar to each other compared to pre-pandemic years.[286] These data are potentially of concern given the increased risk of varicella-related complications for infants and older children. In Ireland, the absolute numbers of hospitalisations for varicella decreased significantly during the pandemic years of 2020 and 2021, with numbers increasing in 2022 and reaching a nine year high (in absolute terms) in 2023 (Section 1.3.2.2). The lasting impact of the interruption of typical VZV transmission during the COVID-19 pandemic possibly remains to be seen. As a result, the ongoing monitoring of the burden of varicella is important to inform decisions on the potential introduction of childhood varicella vaccination programmes in countries where they are currently not in place.

6.3.5 Public health policy decision-making

As outlined in Chapter 1, the research presented in this thesis formed a significant part of a HTA that was submitted as advice to the Minister for Health and to the Health Service Executive in Ireland in July 2023. At the time of writing, the Minister for Health has advised (via a response to a Parliamentary Question on 20 March 2024) that having considered the findings of the HTA he has approved the introduction of the varicella vaccine to the primary childhood immunisation programme, subject to funding being made available via the 2025 Budget Estimates process.[290]

6.4 Reflections and considerations for future research

This thesis entailed a comprehensive evidence synthesis including an economic analysis, to enable evidence-based decision making regarding a public health policy decision to add varicella vaccination to the childhood immunisation schedule in Ireland. In conducting this research, a number of considerations for and general reflections on future research have been identified.

6.4.1 Evolving evidence base

The evidence to support national immunisation programmes continues to evolve and requires regular review. With time, and as a growing number of countries introduce universal childhood varicella vaccination, more data on the long-term effects (effectiveness, safety and waning immunity) of varicella vaccination should emerge. These data provide the basis to update systematic reviews on clinical effectiveness and safety, and economic evaluations of vaccination programmes. Additionally, any changes in the epidemiology of varicella or the understanding of the epidemiology and the resulting impact on healthcare utilisation may provide the basis on which to update economic evaluations. In the event of changes to the epidemiology of varicella, timely access to relevant up-to-date epidemiological and health resource use data would be required. Currently, both a monovalent varicella only and quadrivalent MMRV vaccine are licensed for the prevention of varicella in Europe. However, vaccine development is an ongoing process that involves the development

of both new vaccines and new vaccine types. The application of new technologies to the vaccine development process and the speed with which this can be done was evident in recent years with the rapid development of the mRNA-based vaccines for SARS-CoV-2. As a result, new varicella vaccines may be developed over time also requiring de novo assessments of clinical effectiveness, safety and cost effectiveness.

It has been argued that in the case of new health technologies, economic evaluation conducted as part of HTA should be an iterative process, commencing in the early developmental stage of the technology and continuing through the following three stages: maturing innovation, close to widespread diffusion and moving into practice.[291] Where consideration is being given to reimbursing newly developed health technologies, including vaccines, there may be merit in adopting this approach. However, with an already authorised vaccine, albeit with an evolving evidence base around clinical effectiveness and safety, the timing of the HTA and associated economic evaluation will often be dictated by health policy decision makers. Such HTA requests from decision makers may be influenced by political pressure and include constraints relating to time, financial resources and political feasibility, making it challenging, or even unfeasible, to support an iterative process.[292]

Currently, a systematic review of the clinical effectiveness and safety of a health technology is typically recommended to inform the data inputs for the economic modelling of a health technology.[129] Depending on the quality and timing of any relevant published synthesis of the evidence and the quantity of new evidence, this can be a time-consuming process that adds to the timeline of the economic modelling analysis. To expedite public health policy decision-making and the process of conducting and updating economic evaluations of established health technologies with an evolving evidence base of clinical effectiveness and safety, living systematic reviews may be helpful. They may be particularly useful if numerous country-level decisions are contingent on the findings. A living systematic review is defined as a systematic review which is continually updated, incorporating relevant new evidence as it becomes available.[293] Living system reviews for authorised vaccines would thus enable both new and existing economic evaluations to be updated with the most-up-

date evidence of clinical effectiveness and safety, without the need to conduct a de novo systematic review. This could expedite the process of conducting new or updating existing economic evaluations of established health technologies.

6.4.2 Reporting in research studies

In the context of ongoing and regular review of the evidence base to support vaccination strategies, reporting issues identified in a number of chapters of this thesis warrant highlighting. This is to aid both researchers involved in conducting these reviews and reviewers responsible for assessing papers for publication. The poor quality of reporting of included studies in systematic reviews was identified in Chapters 2, 3, and 4. While systematic reviews are deemed at the upper end of the hierarchy of evidence for research studies, the findings in the aforementioned chapters highlight that systematic reviews are not all created equal and quality can vary significantly. In Chapters 2 and 3, specific issues were identified in terms of the lack of detail in the reporting of relevant data, particularly the detail regarding the intervention. These data, recognised as important in evaluating vaccine effectiveness and safety, include the type of vaccine, vaccine dosage, age at vaccination, interval between doses, brand, and follow-up period. By extension, poor and insufficient reporting of some of these data impacts on the accuracy and accessibility of data required to populate economic models. Quality appraisal tools for systematic reviews, such as AMSTAR 2, include an item specifically relating to the description of included studies, including the intervention.[155] AMSTAR2 guidance advises that these data are required to determine the extent to which the results of different studies should be combined, help explain heterogeneity and assist in the application of the results. Similarly, guidelines for the reporting of systematic reviews, such as PRISMA 2020, include an item for listing and defining data, including intervention characteristics, so that readers have a clear understanding of the information sought.[157] In the first instance, researchers conducting both primary studies and systematic reviews have a responsibility to ensure that relevant data are reported in sufficient detail. In the second instance, reviewers of papers that are submitted for publication have a role in identifying and combatting poor reporting of relevant data. As identified elsewhere, the development and application of reporting guidelines

specifically for studies of the efficacy, effectiveness and safety of vaccines, may be warranted and may be helpful to support improved reporting of relevant intervention data for vaccine studies.[294] Additionally, for the purpose of supporting national immunisation policy, perhaps a centralised approach for conducting systematic reviews of the clinical effectiveness and safety of vaccines, designed by the likes of National Immunisation Technical and Advisory Groups (NITAGs), could be helpful in ensuring that at a minimum standardised dataset is extracted.

6.4.3 Epidemiology of varicella zoster virus

There are a number of aspects of the epidemiology of VZV that are associated with substantial uncertainty or are not clearly understood, creating challenges in modelling VZV transmission and the impact of an intervention such as vaccination. Within the CUA conducted as part of this thesis, the associated modelling parameters included the probability that a susceptible person becomes infected given contact with an infectious person, the reactivation rate of VZV leading to herpes zoster, and the rate of exogenous boosting against herpes zoster. These parameter values were estimated through model calibration or were assumed using data extracted in the review in Chapter 4. Two of these parameters, namely the probability that a susceptible person becomes infected with varicella given contact with an infectious person and the reactivation rate of VZV leading to herpes zoster, are derived from processes that we know exist. However, the same cannot be said about the exogenous boosting effect of VZV. In 1965, Hope-Simpson hypothesised that immunity to VZV reactivation is boosted through exogenous exposure to wild type VZV.[295] Despite the lack of evidence to support its existence, the hypothesis has nevertheless influenced past policy decisions on the introduction of childhood varicella vaccination in a number of countries.[296, 297] More recently, data from the USA have demonstrated that the predicted increase in incidence of herpes zoster among adults due to a decrease in the exogenous boosting effect, following the introduction of universal childhood varicella vaccination, has not materialised.[226, 274] If the exogenous boosting effect of VZV exists, an important equity concern arises in the context of varicella vaccination; the introduction of a varicella vaccination program could possibly protect the health of one population group (children) at the

expense of another (adults).[298] Without examining the different ethical perspectives that could be adopted on this issue, some may offer justification for introducing vaccination while others a basis for the case against introducing it. Some studies adopt a clear stance on the issue and argue that it is unjust to withhold beneficial vaccination from children in order to benefit others in society.[299, 300] Others offer that vaccination policy should not be viewed as a clash between different age cohorts looking out for their own interests. It is argued that varicella vaccination policies should be set by individual societies as a whole based on their own health care system, values or assessment of the evidence.[301] Given the effect of exogenous boosting has not yet been observed, it is likely that if such an effect exists, it is very small. In contrast, the effect of varicella vaccination has been demonstrated and is large. Therefore, it may be questionable to allow a policy to be dictated by an unproven theory, in light of the demonstrated substantial benefits associated with vaccination. As such, and in light of the uncertainty as to the existence of the theory, where a decision on the introduction of childhood varicella vaccination is influenced by the exogenous boosting hypothesis, the ethical consequences of such a decision should be thoroughly examined.

6.4.4 Perspective adopted in economic evaluations

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.[130] In line with the results from Chapter 4 and calls for economic evaluations of vaccines to adopt a broader perspective than the healthcare payer perspective in order to incorporate their full value,[132, 200, 218, 302] the CUA conducted as part of this thesis adopted the payer perspective in the base-case scenario and the societal perspective in a scenario analysis. The results of the CUA highlight the extent to which the outcome of a CUA may differ depending on the perspective adopted. From the payer perspective, the ICERs for one-dose (versus no vaccination) and two-dose long interval (versus one-dose vaccination) strategies were €8,712 and €45,090 per QALY gained, respectively. From the societal perspective, both one- and two-

dose strategies dominated (less costly and fewer QALY losses) no vaccination. While the guidance in Ireland provides for the possibility of adopting a wider perspective, it states that this must be clearly justified and supported by sufficient evidence.[130] Arguably the national guidance lacks clarity as to the definition of 'sufficient evidence' and this may differ depending on the particular disease and intervention under consideration. This could possibly lead to uncertainty for the analyst as to whether or not to widen the perspective, resulting in inconsistencies in terms of the perspective(s) that is (are) adopted in such analyses. In turn, this has the potential to impact on policy decisions that are informed by such analyses. Additionally, given that public health budgets worldwide are under ever increasing demands, with many health technologies competing for scarce funds, perhaps there should be consistency with respect to the perspective(s) from which all interventions are assessed in economic analyses.

6.5 Strengths and limitations

The strengths and limitations of each study included in this thesis have been presented in Chapters 2 to 5. Further strengths and limitations of the overall thesis are described below.

6.5.1 Strengths

The research presented in this thesis has a number of strengths relating to the rigour of the methods employed and wider contributions to the scientific literature. The research is underpinned by analytical tools that are widely recognised as evidence generators to inform evidence-based public health policy.[3, 116] It includes two comprehensive overviews of reviews of the clinical effectiveness and safety of childhood varicella vaccination. The reviews were planned using a pre-specified protocol,[303] and reported in accordance with accepted international standards.[157] The reviews include a thorough assessment of the systematic review evidence that has been generated globally since the monovalent varicella vaccine was developed almost 50 years ago. The reviews have the benefit of leveraging off existing reviews rather than re-extracting and analysing the primary data. They capture changes in

varicella vaccination that have occurred over time, including changes to the number of recommended vaccine doses and the development of the quadrivalent MMRV vaccine and thereby the evolution of established universal childhood varicella vaccination programmes. The strength of the findings in Chapters 2 and 3 are demonstrated by both the large number of primary studies within the included systematic reviews (15 RCTs and 206 other primary studies/reviews for vaccine effectiveness; 34 RCTs and 62 other primary studies/reviews for safety) and the consistency of the evidence, which in turn serves to reinforce the findings of this thesis. Additionally, the evidence from the included reviews originates from many regions and countries, ensuring that the results are broadly generalisable. As novel contributions to the already extensive literature in this area, these reviews are the first to synthesise the large body of systematic review evidence that has been generated over the past five decades on the clinical effectiveness and safety of childhood varicella vaccination.

Chapter 4 provides a comprehensive update and assessment of the literature on the methodology for the economic modelling of childhood varicella vaccination. It updates the evidence base by 10 years and ensures that the most up-to-date evidence was used to inform the economic modelling conducted in Chapter 5. To the best of my knowledge, Chapter 5 reports the first CUA of universal childhood varicella vaccination in Ireland, incorporating both varicella and herpes zoster diseases. The CUA was enabled by the development of a de novo population-based epidemiological model of VZV transmission in Ireland. In addition to comparing varicella vaccination with no vaccination, the CUA is one of few international studies that conducts incremental analyses comparing the cost effectiveness of alternative varicella vaccination strategies with each other. This included important comparisons of the cost effectiveness of strategies with potentially significant differences in underlying programme costs, for example two-dose versus one-dose. Additionally, the analysis was conducted from both the payer and societal perspectives. This enabled an estimation of the wider societal impact of varicella, beyond those who

are ill with the disease, and the resulting impact on the cost effectiveness of the intervention.

Due to its potential impact on incidence of herpes zoster, the exogenous boosting hypothesis has been a concern in considerations regarding the introduction of universal childhood varicella vaccination programmes. This concern has been influential in decisions to not introduce childhood varicella vaccination in countries including the UK and Norway.[296, 297] Given that there is substantial uncertainty associated with the theory, its inclusion in the model requires assumptions about its effect that are unsupported by clear evidence. In turn, this gives rise to challenges in interpreting model results that incorporate it. Long-term follow up data from the USA, which has the longest running childhood varicella vaccination programme, have shown that the predicted increased incidence of herpes zoster among unvaccinated adults has not materialised.[226, 274] For these reasons, exogenous boosting was considered as a scenario analysis in this model, ensuring that the base case model results could be clearly interpreted.

This thesis involves current Irish policy-relevant research conducted as part of a HTA. The findings will inform a health policy decision regarding the potential introduction of an intervention for a disease that affects a considerable number of children and their families in Irish society each year. Regardless of whether the decision is to introduce universal childhood varicella vaccination, or not, the decision will be impactful and will have long-term implications for society. In terms of the reach and accessibility of this research, all three published papers are available via open access. The findings from Chapters 2, 3 and 4 are relevant and generalisable to other countries where a decision to introduce universal childhood varicella vaccination or a change to an existing programme is being considered. While the ICERs from the CUA may not be generalisable to other countries, the methods applied in the economic modelling and analysis are transferrable. Additionally, the overall findings from Chapter 5 are relevant in other countries where the cost effectiveness of universal childhood varicella vaccination is being assessed.

6.5.2 Limitations

There are several limitations with regards to the methods used and quality of data in this thesis that warrant consideration. While the overview of reviews approach benefits from leveraging off existing systematic reviews, if the underlying reviews are of poor quality, the interpretation of the evidence may be at risk of bias and a misleading representation of the evidence base. The majority of systematic reviews included in both overviews of reviews of were considered to be of 'critically low' quality using the AMSTAR 2 tool. However, the included reviews were published over 20 years, during which time the methodology for systematic reviews has evolved and become increasingly formalised. The *Cochrane Handbook for Systematic Reviews of Interventions*, which describes in detail the methods used in Cochrane system reviews, was originally published in 2003 with the most recent update in August 2023.[304] Similarly, the *Joanna Briggs (JBI) Institute Manual for Evidence Synthesis* is continuously being updated to include developments and updates to JBI methodologies and methods for evidence synthesis.[305] Additionally, the ongoing development and application of reporting guidelines, including the PRISMA guidelines for systematic reviews[157] and more recently the Preferred Reporting Items in Overviews of Reviews (PRIOR) guidelines for overviews of reviews,[306] mean that more recent reviews tend to have higher quality ratings when assessed using tools such as AMSTAR 2.

While systematic reviews are intended to be carried out objectively, it cannot be guaranteed that all reviewers will make the same decisions when conducting reviews. That and the motivations for a systematic review can impact on the data extracted and the outcomes and overall findings reported. Although the systematic reviews included in the overviews of reviews may have aimed to do what was required for inclusion, they may not have been conducted in the same manner or even drawn the same conclusions if conducted by another reviewer. This limitation could also lead to bias in the interpretation of the evidence and a misleading representation of the evidence base. In the case of the overviews of reviews conducted in this thesis, this risk is considered low given the consistency of findings reported across reviews.

At the time the overviews of reviews were conducted, a protocol for the development of a reporting guideline for overviews of reviews of healthcare interventions had been published.[307] However, the final paper on the PRIOR guidelines was not published until after the overview of reviews were completed[306] and therefore they were reported in line with the PRISMA guidelines.[157] A subsequent comparison of the PRISMA and PRIOR guidelines identified that item number 17 in the PRIOR guidelines, relating to primary study overlap, was the only new item in the PRIOR guidelines. An assessment of primary study overlap conducted as part of the overviews of reviews (sections 2.3.5 and 3.3.5) and a post hoc review of the PRIOR guidelines suggests that the reporting of the overviews of reviews is aligned with the PRIOR guidelines.

In line with international practice on the economic modelling of childhood varicella vaccination reviewed as part of this assessment (Chapter 4), a dynamic transmission model approach was used in the economic modelling. Notwithstanding the appropriateness of model choice for the economic evaluation, economic models in general have several important limitations. Firstly, they seek to model disease and intervention pathways in a manner resembling the typical experience of individuals. Therefore, in order to feasibly develop a model, a range of structural assumptions are generally made. While these assumptions may result in the exclusion of some relevant risks and outcomes, such as the risk of reinfection or the risk of mortality directly attributable to the disease as was the case in this model of varicella vaccination, they also reduce the complexity of the model and may reduce the reliance on parameter estimates that are supported by weak or limited evidence. This leads to another important limitation, namely that a model is only as reliable as the data underlying it. As outlined in Chapter 1, economic modelling studies generally carry a heavy data burden and evidence typically originates from multiple sources. The economic model consisted of a large number of parameters that were derived from numerous sources and were combined to estimate the epidemiological and economic effects of vaccination. While the data underpinning each parameter were assessed for plausibility, quality, and applicability, some were based on limited evidence. These limitations of the data highlight the importance of conducting

comprehensive uncertainty analysis in any economic modelling study, not least in studies informing public health policy decision-making. As was done in this thesis, an economic modelling study should include a range of both sensitivity and scenario analyses as appropriate.

6.6 Conclusions

Through a comprehensive evidence synthesis, including a de novo economic analysis, this thesis adds to the global evidence base on the clinical effectiveness, safety and cost effectiveness of childhood varicella vaccination. The findings from two overviews of reviews, that cover an evidence base from systematic reviews over a 20 year period running from 2001 to 2021, firmly establish that childhood varicella vaccination is both effective and safe. Although both one- and two-dose vaccination were found to be similarly highly effective in preventing severe varicella, two-dose was shown to be more effective in preventing varicella of any severity.

Evidence from a synthesis of the international literature on the methodology for the economic modelling of childhood varicella vaccination, informed the overall modelling approach for conducting a de novo economic evaluation of universal childhood varicella vaccination in Ireland. The modelling approach included the development of a dynamic transmission model of VZV for Ireland that was used to analyse the impact of varicella vaccination. The findings from an Irish-specific CUA suggest that from the payer perspective, one-dose vaccination would be cost effective, compared with no vaccination, at a willingness-to-pay threshold of €20,000 per QALY gained. The incremental cost-effectiveness ratios for two-dose strategies, versus one-dose, were approximately €45,000 per QALY gained. From the societal perspective, universal childhood varicella vaccination would be cost-saving with the two-dose short interval strategy dominating all others, generating the largest cost-savings and largest QALY gains. The results of the economic analysis were robust to sensitivity and scenario analyses.

At the time of writing, the findings from this thesis have had an impact on childhood vaccination policy in Ireland. The HTA conducted by HIQA, which includes the

evidence from Chapters 2 to 5 inclusive of this thesis, has informed a decision by the Minister for Health to approve the introduction of varicella vaccination to the childhood immunisation programme. This approval, noted in response to a Parliamentary Question in March 2024, is subject to funding being made available via the 2025 Budgetary Estimates process.

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Supplementary Appendix for Chapter 2

Appendix A 2.1 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) Searched first five pages (100 results) and selected the option: 'sort by relevance' and used the limiter: Any type 'Review'.		100

The grey literature search included the Trip medical database, 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,[308] and websites of a number of international health agencies.

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*) 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)" Search limited to 1,000 hits per website and filetype 'pdf'.		1,000

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 Health 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

Country	Name of Agency/Unit/Ministry	Website domain
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	Mnistry 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
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

Country	Name of Agency/Unit/Ministry	Website domain
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
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

Country	Name of Agency/Unit/Ministry	Website domain
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
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

Country	Name of Agency/Unit/Ministry	Website domain
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 Clincal 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

Country	Name of Agency/Unit/Ministry	Website domain
International	Centers for Disease Control and Prevention	cdc.gov

Appendix A 2.2 Excluded studies retrieved from databases, registries and grey literature sources

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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
13	Varicella and rotovirus vaccination in New Zealand - assessment reports	New Zealand National HealthCommittee	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
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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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-	Not a systematic review

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
				june2014-references.pdf?sfvrsn=31c10d0a_2	
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
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

Study Number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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 A 2.3 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Al Kaabi[170] 2020 10.1080/21645515.2019.1638726 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA Database inception to 1 February 2016	Individuals ≥12mths 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)) Studies varied greatly in terms of size, with samples ranging from 102 to 20,788 patients. Turkey (n=7 studies); Saudi Arabia (n=2); Abu Dhabi, United Arab Emirates (UAE) (n=1)	One-dose Turkey (vaccine type NR)	Total: 10 observational studies (study type not reported)	NR and unvaccinated	≥5yrs in one study (Turkey). Others: NR	Incidence of varicella Varicella associated complications Varicella associated hospitalisation Long-term persistence of protection based on incidence of breakthrough varicella over time	Incidence of varicella <u>Children aged 2-15.5yrs</u> (per 100,000 patient yrs.) Vaccinated: 4,550 Unvaccinated: 12,020 Incidence and risk of varicella <u>Preschool children (n=124) in an outbreak)</u> Vaccinated (1-dose): 24% had varicella Unvaccinated: 34% had varicella Risk 3.5 times higher in children vaccinated ≥5yrs versus those vaccinated more recently. Complications with varicella <u>Non-hospitalised children in an outbreak</u> Vaccinated: no complications Unvaccinated: 20.3% secondary skin infections, 18.6%	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 Not conducted Overall quality of evidence assessment 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
							vomiting, 11.8% diarrhoea, 6.7% vertigo and 5% pneumonia. Hospitalisation with varicella <u>Incidence in children aged 1-5yrs</u> (per 100,000 children per year) Pre-UVV: 6.1 to 9.1 Post-UVV: 3.1 to 4.3 <u>Children (% hospitalised)</u> Vaccinated: 0.20% Unvaccinated: 0.60% <u>Mean age of hospitalised children</u> Pre-UVV: 48.6mths Post-UVV: 52.8mths (mean age of hospitalised children was older post-UVV, p<0.005) Hospitalisation and complications with varicella <u>Children</u> The proportion of children hospitalised with varicella and neurological complications was not significantly lower post-UVV versus pre-UVV.		

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
							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. The percentage of children with seizures (including febrile seizures) was significantly reduced post-UVV versus pre-UVV.		
		Two-dose Abu Dhabi, UAE and Saudi Arabia (vaccine type NR)				Incidence of varicella	Incidence of varicella (per 100,000 population) <u>Abu Dhabi</u> Pre-UVV (2011): 486 Post-UVV (2013): 147 to 168		

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
							<u>Saudi Arabia</u> Pre-UVV (1994): 739.8 Post-UVV (2011): 88.1 <u>Saudi Arabia armed forces hospital</u> Pre-UVV (2007): 754 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Arlant[171] 2019 10.1186/s12889-019-6795-0 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA 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 Costa Rica (from 2007) Coverage: 76% in 2008; 95% in 2015. Uruguay (One-dose from 1999. Two-dose from 2014 but no data on impact of two-dose) Coverage: 90% shortly after UVV introduction and maintained until 2013.	Total: 4 observational studies Study type: not clear Costa Rica (n=1 study) Uruguay (n=3 studies)	Not vaccinated	Up to 7yrs post UVV introduction in 1 study (Costa Rica) Up to 14yrs post UVV introduction in 1 study (Uruguay) Others: NR	Incidence of varicella Ambulatory visits associated with varicella Hospitalisation associated with varicella Complications with varicella Mortality associated with varicella	Costa Rica Incidence of varicella (Costa Rica) 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. Hospitalisation associated with varicella (Costa Rica) 86% reduction in varicella hospitalisations reported (87% in children aged <5yrs) for the post- (2008–2014) versus pre- (2000–2007) UVV era. Hospitalisations for complicated varicella decreased by 98%: 53 hospitalisations due to varicella complications (pneumonia, meningitis, or encephalitis) in 2008 versus one in 2014. Mortality associated with varicella (Costa Rica) Pre-UVV (2000-2007): n=23 deaths	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. For countries that have already implemented UVV, the challenge is to maintain high rates of coverage and, where relevant, consider inclusion of a second dose to reduce breakthrough cases.	Risk of bias Not conducted Overall quality of evidence assessment 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
							Post UVV (2008-2014): n=24 deaths Therefore showing no evident difference. However no information was available on the vaccination status of the deceased patients.		

							Uruguay Incidence of varicella (Uruguay) 2009: 10yrs post-UVV, incidence was 20/100,000 population. 2013 (outbreak): Among 151 cases of varicella infection detected in educational centres of one department, 97% were in vaccinated children. Ambulatory visits associated with varicella (Uruguay) 2005: 6yrs post-UVV, incidence of ambulatory visits by children recorded by private insurance companies reduced by 87% compared to pre-UVV. Visits reduced by 80, 97, 81 and 65% in the <1, 1-4, 5-9 and 10-14yrs age groups respectively. Hospitalisation associated with varicella (Uruguay) 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. Complications with varicella (Uruguay) 1997-2005 (n=294,831 patients): 7% of children with breakthrough varicella had		

							complications, compared with 12% of unvaccinated children. 2013 (outbreak): Among 151 cases of varicella infection detected in educational centres of one department, 97% were in vaccinated children. There were no serious cases and frequency of complications was low (4%).		

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 Brazil (One-dose from 2013. Two-dose from 2018 but no data on impact of two-dose)	Total: 3 studies Case-control (n=1) Others: study type not clear	Not vaccinated		Incidence of varicella Incidence of breakthrough varicella Vaccine effectiveness any severity and moderate/severe varicella	Brazil Incidence of varicella <u>Florianapolis, Brazil (children aged <2yrs vaccinated)</u> 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. <u>Sao Paulo, Brazil</u> Incidence from 2002 to 2017 (annual cases) show a trend to increasing numbers of cases up to introduction of vaccination in 2013: Pre-UVV (2013): n=25,052 Post-UVV (2017): n=2,822 Vaccine effectiveness <u>Sao Paulo, Brazil (case-control study of children vaccinated with one-dose at 15mths)</u> VE in 15-35mth olds against any severity varicella: 86% VE in 15-35mth olds against moderate/severe varicella: 93% Breakthrough rate: 22% - possibly attributable to vaccine failure, as the cases had been vaccinated		

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
							only 9mths before, on average; patients with breakthrough varicella had less severe disease than non-breakthrough cases.		
		One-dose and two-dose monovalent Puerto Rico (one-dose from 1996 and two-dose from 2007)	Total: 1 study Study type: not clear	Not vaccinated	Up to 17yrs post UVV introduction	Hospitalisation associated with varicella	Puerto Rico Morbidity associated with varicella 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Bayer[164] 2007 10.1016/j.vaccine.2007.07.010 LMUinnovativ (Ludwig-Maximilians University) research priority Project MCHealth 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) Outbreaks setting in day care centres or elementary schools	One-dose	Total: 14 studies Study type unknown	No vaccination	Unclear	Vaccine effectiveness (VE) for prevention of varicella‡ ‡ 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 (model unclear) Overall (n=16 estimates): 72.5% (68.5 to 76%) 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 Not conducted Overall quality of evidence assessment Not conducted
	Subgroup analysis								
	n=918 children, median age 6mths-12yrs	One-dose	Total: 4 studies 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 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 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**
Author Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Benchimol[176] 2021 10.1093/jcag/gwab015 and 10.1053/j.gastro.2020.12.079 Guideline was funded by the Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes, and CANImmunize. 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	Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy with the associated systematic review based on the general population (see below) (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 (vaccine type not reported)	Total: 2 studies Systematic reviews (SR): n=2 (1 SR includes a further 2 SRs) Effectiveness outcome: 4 SRs of 42 observational studies Safety outcome: 7 RCTs and 5 observational studies	No vaccination	NR	Vaccine effectiveness (VE) against all varicella VE against moderate/severe varicella	Pooled VE (95% CI) in preventing varicella infection in healthy children 1 SR reported VE of 81% (78 to 84%) Pooled VE (95% CI) in preventing moderate/ severe varicella infection in healthy children VE 98% (97 to 99%)	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 Cochrane RoB for RCTs and ROBINS-I for non-randomised studies Assessment for individual studies not provided. Overall deemed 'not serious' for effectiveness studies relating to healthy children in the general population. Overall quality of evidence assessment Effectiveness GRADE certainty of evidence (CoE) for effectiveness was anchored to the general population (healthy children), adapted from
		Two-dose (vaccine type not reported)				VE against all varicella	Pooled VE (95% CI) in preventing varicella infection in healthy children 1 SR reported VE of 92% (88 to 95%)		

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
supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program. 1989 to 12 April 2019									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 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Di Pietrantonj[159] 2021 10.1002/14651858.CD004407.pub5 National Institute for Health Research (NIHR) via the NIHR Cochrane Incentive Award Scheme 2018 - 128383 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. RCTs only: Approximately 3,000 healthy children aged 11-22mths at vaccination with MMR or MMRV/MMR+V vaccine.	One-dose monovalent Varivax (n=1) Multiple (n=1)	Total: 2 studies Case control (n=2)	No vaccination	NR	Vaccine effectiveness (VE) against varicella‡ – any severity ‡defined in this review as clinical and/or laboratory-confirmed	Pooled VE (95% CI) against <u>any severity varicella</u> (random effects model) ¥ Overall (n=2 estimates): 86% (78 to 92%, I^2=0%) ¥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. More evidence is needed to assess whether the protective effect of MMRV	Risk of bias Risk of bias conducted for all primary studies. RCTs assessed using criteria adapted from the *Cochrane Handbook for Systematic Reviews of Interventions* Case-control (prospective and retrospective) and cohort studies assessed using the appropriate Newcastle-Ottawa Scales. Case-only ecological method studies, self-controlled
		One-dose monovalent (Varilrix) (varicella vaccine administered with 2nd dose MMR)	Total: 3 studies RCT (n=3)	2-dose MMR vaccine (no varicella vaccination)	Up to 5yrs; 5-10yrs; Up to 10yrs	VE against varicella - any severity Long-term persistence of protection against varicella - any severity	Pooled VE (95% CI) against <u>any severity varicella</u> (random effects models) Overall (up to 10yrs) (n=3 estimates): 67% (64 to 70%, I^2=0%) 5yrs (n=1 estimate): 65% (57 to 72%) 5-10yrs (n=1 estimate): 67% (62 to 71%) 10yrs (n=1 estimate): 67% (62 to 71%)		
						Vaccine effectiveness (VE) against varicella – moderate/severe Long-term persistence of protection against varicella – moderate/severe	Pooled VE (95% CI) against <u>moderate/severe varicella</u> (fixed effects model) Overall (up to 10yrs (n=3 estimates): 90% (88 to 92%, I^2=0%) 5yrs (n=1 estimate): 91% (86 to 94%) 5-10yrs (n=1 estimate): 90% (87 to 93%) 10yrs (n=1 estimate): 90% (86 to 92%)		

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: 1 study RCT (n=1)		5-10yrs	Long-term persistence of protection against varicella – severe	VE (95% CI) against <u>severe varicella</u> (fixed effects model) Overall (n=1 estimate): 95% (53 to 99%)	could wane with time since immunisation.	case series and person time cohort studies assessed for *case selection, exposure, observation and exposure risk period and comparability*. <u>Efficacy/ Effectiveness studies</u> 8/14 (57%) varicella studies rated 'low', 4 (29%) rated 'unclear' and 2 rated 'high' (14%) risk of bias. Overall quality of evidence assessment GRADE Quality of
		One-dose quadrivalent MMRV ProQuad (n=1) MMRV Priorix-Tetra (n=3)	Total: 4 studies Cohort study (n=4)	No vaccination	NR	Vaccine effectiveness (VE) against varicella - any severity	Pooled VE (95% CI) against <u>any severity varicella</u> (random effects model) Overall (n=4 estimates): 75% (41 to 89%, I^2=98%) MMRV ProQuad (n=1 estimate): 94% (92 to 96%) MMRV Priorix-Tetra (n=3 estimates): 62% (61 to 63%)		
		Two-dose monovalent Varivax (n=1) Multiple (n=1)	Total: 2 studies Case control (n=2)	No vaccination	NR	VE against varicella – any severity	Pooled VE (95% CI) against <u>any severity varicella</u> (random effects model) Overall (n=2 estimates): 95% (86 to 99%, I^2=0%)		
		Two-dose quadrivalent MMRV Priorix-Tetra	Total: 2 studies Cohort study (n=2)	No vaccination	NR	Vaccine effectiveness (VE) against varicella - any severity	Pooled VE (95% CI) against <u>any severity varicella</u> (random effects model) Overall (n=2 estimates): 87% (86 to 87%, I^2=0%)		
		Two-dose quadrivalent MMRV Priorix-Tetra	Total: 3 studies RCT (n=3)	2-dose MMR vaccine only (no varicella vaccine)	Up to 5yrs; 5-10yrs; Up to 10yrs	Long-term persistence of protection against varicella - any severity	VE (95% CI) against <u>any severity varicella</u>: (random effects model) 5yrs (n=1 estimate): 95% (92 to 97%) 5-10yrs (n=1 estimate): 95% (94 to 96%) 10yrs (n=1 estimate): 95% (94 to 96%)		

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
						Long-term persistence of protection against varicella – moderate/severe	VE (95% CI) against <u>moderate/severe varicella</u>: (random effects model) 5yrs (n=1 estimate): 100% (98 to 100%) 5-10yrs (n=1 estimate): 99% (98 to 100%) 10yrs (n=1 estimate): 99% (98 to 100%).		Evidence assessment applied for RCTs examining VE against varicella of 2-dose MMRV and 1-dose MMR+V. Certainty of evidence rated as HIGH.
		At least one-dose monovalent Varivax (n=1) Not defined (n=1)	Total: 2 studies Case control (n=2)	No vaccination	Unknown	VE against varicella – any severity	Pooled VE (95% CI) against <u>any severity varicella</u> (random effects model) Overall (n=2 estimates): 88% (82 to 92%, I^2=0%)		
		At least one-dose quadrivalent MMRV Priorix-Tetra	Total: 1 study Case control (n=1)			VE against varicella - any severity	VE (95% CI) against <u>any severity varicella</u> (random effects model) Overall (n=1 estimate): 86% (72 to 93%)		
						VE against varicella – moderate/severe	VE (95% CI) against <u>moderate/severe varicella</u> (random effects model) Overall (n=1 estimate): 93% (83 to 97%)		
		At least one-dose quadrivalent MMRV	Total: 2 studies COEM study (n=2)			VE against varicella incidence (by age group)	VE (95% CI) against <u>incidence of varicella</u> (random effects model) Overall (n=5 estimates): 76% (57 to 86%, I^2=100%) Age <1yr (n=1 estimate): 83% (76 to 88%) Age 1-4yrs (n=1 estimate): 92% (91 to 93%) Age 5-14yrs (n=1 estimate): 86% (84 to 88%) Age 0-14yrs (n=2 estimates): 35% (20 to 47%, I^2=98%)		

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 COEM study (n=3)			VE against hospitalisation with varicella	Pooled VE (95% CI) against hospitalisation (random effects model) Overall (n=7 estimates): 57% (45 to 66%, I^2=60%) Age <1yr (n=2 estimates): 48% (26 to 63%, I^2=0%) Age 1-4yrs (n=2 estimates): 71% (15 to 90%, I^2=88%) Age 5-14yrs (n=2 estimates): 63% (21 to 81%, I^2=68%) 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;

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Garrido[175] 2012 10.32385/rpmgf.v28i2.10928 No funding received January 2005 to November 2009	Healthy children aged 1-12yrs at vaccination 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 Systematic reviews (SRs) (n=3); Meta-analysis (n=1); Primary studies (n=7)	No vaccination or placebo	Various: Up to 10yrs in one clinical trial Up to 3yrs in one primary study Up to 2yrs in one SR	Incidence of varicella Vaccine effectiveness against varicella (any severity) Vaccine effectiveness against varicella (moderate-severe disease) Vaccine effectiveness against varicella (severe disease) Long term persistence of protection based on incidence of breakthrough varicella (BV) over time	Vaccine effectiveness A SR analysing 41 (mostly observational) studies published in the USA concluded that: 1-dose has 80 to 85% effectiveness in preventing <u>any severity</u> chickenpox and >95% in the prevention of <u>severe</u> chickenpox. 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). 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. A SR analysing 17 observational studies concluded that despite 1-dose providing excellent protection (VE 80 to 85% in preventing <u>any severity</u> varicella and 97 to 100% in preventing <u>severe varicella</u>), a higher VE is	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,	Risk of bias Not conducted Overall quality of evidence assessment The Strength of Recommendation Taxonomy (SORT) scale from the American Family Physician Foundation was used. 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).

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
							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. In a SR analysing 1 SR (including 2 RCTs) and another RCT, there were no significant 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. 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%). Long term persistence of protection A meta-analysis based on 14 observational studies of outbreaks in primary schools reported that 9 of the studies	further studies will be needed to assess the effectiveness and long-term impact of varicella vaccination.	The remaining studies were not graded.

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
							evaluated the decrease in immunity over time: 2 studies found no relationship between vaccination time and decreased immunity, but did not specify how they came to that conclusion. 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 A SR reported 2-dose VE of 98.3% (95% CI: 97.3 to 99%) in an observational period of 10yrs.		
		Two-dose (vaccine type not reported)		One-dose (vaccine type not reported)		Incremental vaccine effectiveness (2-dose versus 1-dose)	Incremental vaccine effectiveness 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 Rate of breakthrough varicella	Vaccine effectiveness 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.		

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 effectiveness against varicella (any severity) Vaccine effectiveness against varicella (moderate/ severe) Hospitalisation associated with varicella	The reduction was seen in all age groups. 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%. 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%). 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. Hospitalisation associated with varicella An retrospective study in USA comparing pre- and post-UVV reported: the hospitalisation rate for varicella decreased from 15.7 to 5.5 cases/100,000 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		

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							no significant difference in mean age of children hospitalised 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;

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Goh[172] 2019 10.1080/14760584.2019.1594781 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA 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. Taiwan (n=7 studies); Australia (n=8); South Korea (n=1)	One-dose Taiwan (from 2004) Australia (from 2005) Coverage: 78.4% in 2007 South Korea (from 2005) Coverage: 97% in 2011 (vaccine type not reported)	Total: 16 studies Study type: observational studies/ epidemiological datasets (breakdown not provided)	Pre-vaccination era	10yrs for severe hospitalised varicella (Australia) Others not reported	Incidence of varicella Complications associated with varicella Hospitalisation associated with varicella Mortality associated with varicella	Taiwan Incidence of varicella (Taiwan) Data from 3 studies indicate a 2.9- to 3.8-fold reduction from the post-vaccine era to the UVV era. Hospitalisation associated with varicella (Taiwan) Data on hospitalisations were limited and varied. 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). Admission rate due to varicella increased to 139/10,000 dermatological admissions in the post-vaccination era. 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 ($p < 0.001$). Complications associated with varicella (Taiwan) 1 study reported that the proportion of patients with	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 Not conducted Overall quality of evidence assessment 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
							neurological complications significantly reduced (p=0.01) in the post-vaccine era versus pre-vaccine era. Frequency of pneumonitis increased (p=0.05), in the post-vaccine era versus pre-vaccine era. Mortality associated with varicella (Taiwan) 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. In another study, a lower fatality rate of 0.05% of hospitalised varicella cases was reported during the post-vaccine era, 2000-03.		
							Australia Incidence of varicella (Australia) Increase in incidence post-UVV (2005) from 17.8/100,000 population in 2006 to 19.6/100,000 population in 2008. Grey data from the Australian Department of Health also suggest an increasing trend in varicella incidence. However, the seemingly low number of cases reported highlights potential under		

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
							reporting, reducing confidence in the data. Hospitalisation associated with varicella (Australia) 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. Stepwise reductions observed in the annual incidence of varicella hospitalisation per 100,000 population as follows: pre-vaccination era: 6.1 post-vaccination era: 5.3 UVV era: 2.9 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). 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). Access to vaccine did not seem to influence the duration of hospitalisation, which ranged from 3.3 to 7.4 days.		

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
							South Korea Incidence of varicella (South Korea) Grey data suggest an increasing incidence of varicella post-UVV. 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. 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. 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

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 Year DOI Funding source Search date	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Hong[166] 2017 Article number: 1006-916X(2017) 03-0331-06 http://www.cqvip.com/qk/90851a/201703/672760216.html Funding source not provided Period before 2016	n=46,455 children and students in varicella outbreak clusters in China (involving >20 cases) n=4,613 children and students for case-control studies n=41,842 children and students for cohort studies	One-dose (type not specified)	Total: 18 studies Case-control (n=10) Retrospective cohort (n=8)	No vaccination	<3yrs to 10yrs	Vaccine effectiveness for prevention of varicella‡ ‡Clinically or laboratory diagnosed varicella used in this review	Pooled VE against varicella (95% CI) (fixed effects model) Overall (n=18 estimates): VE 73% (71 to 76%, I^2=22%) Case-control studies (n=10 estimates): VE 70% (66 to 74%, I^2=22%) Cohort studies (n=8 estimates): 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 Not conducted Overall quality of evidence assessment Not conducted
	Subgroup analysis								
	n=1,033 children aged 12mths-3yrs	One-dose (type not specified)	Total: 2 studies Retrospective cohort (n=2)	No vaccination	<3yrs	Vaccine effectiveness for prevention of varicella	Pooled VE against varicella (95% CI) (fixed effects model) VE 98% (95 to 99%, I^2=38%)		
	n=1,115 children aged 4-6yrs		Total: 3 studies Retrospective cohort (n=3)		3-5yrs		Pooled VE against varicella (95% CI) (fixed effects model) VE 92% (87 to 95, I^2=58%)		
	n=881 children aged 7-9yrs		Total: 3 studies Retrospective cohort (n=3)		6-8yrs		Pooled VE against varicella (95% CI) (fixed effects model) VE 70% (45 to 83%, I^2=17%)		
	N=464 children and students		Total: 2 studies Retrospective cohort (n=2)		9-10yrs		Pooled VE against varicella (95% CI) (fixed effects model) VE 54% (-2.0 to 58%, I^2=0%)		

Key: CI – confidence interval; 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Kaufmann[88] 2020 10.1080/14760584.2020.1825947 GlaxoSmithKline Biologicals SA 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: One-dose monovalent (regional implementation since 2003; regional recommendation until 2017) 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 In a number of pilot regions, incidence decreased by 30-80% depending on coverage. In 2 regions (Sicily and Puglia), incidence decreased by ≥89%. 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. Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively. Different benefit-risk evaluations of a quadrivalent (MMRV) vaccine used as a first dose led to different recommendations (MMRV	The 'Cochrane grading system for bias' was used, although not clear what tool was used:* Low risk of bias (n=74) Unclear risk of bias (n=8) High risk of bias (n=41) * Review included a total of 123 studies, not all of which were relevant for this overview of reviews. The analysis focused primarily
			Study type: NR (n=2) Data sources: Surveillance/ hospital and regional database	No vaccination	Within 4yrs after UVV introduction	Hospitalisation associated with varicella	Hospitalisation associated with varicella 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		

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
							UVV regions (p=0.0428 and 0.0427, respectively). 2 other regions (Tuscany and Puglia) reported decreases in varicella-related hospitalisation of 44% and 26% respectively, within 4yrs following introduction of UVV.	versus MMR+V) in these countries. ‡Moderate and severe varicella not defined.	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. Overall quality of evidence assessment Not conducted
			Study type: NR (n=1) Data source: Epidemiological/ hospital records	No vaccination	Within 4yrs after UVV introduction	Complications associated with varicella	Complications associated with varicella 1 region reported a decrease in complications from 57 cases in 2002 to 14 in 2007.		
		Germany: One-dose monovalent from 2004 and quadrivalent MMRV from 2006 (national implementation since 2004) Coverage: After the introduction of the 1-dose varicella UVV program, coverage rates generally increased year by year up to 65%.	Surveillance studies (n=3) Others (study type NR) (n=4)	No vaccination	Up to 10yrs post vaccination	Incidence of varicella Vaccine effectiveness against varicella	Incidence of varicella 2 surveillance studies demonstrated that 1-dose UVV decreased incidence by approx. 63–75% in children ≤4 years of age. At a regional level, significant decreases in varicella incidence were also reported in Munich, Bavaria. Vaccine effectiveness 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. VE 72% (95% CI: 59-81%, p< 0.001)) based on a surveillance study of outbreaks in day-care		

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							centres, with no difference by age, day-care centre, or gender. 1-dose was shown to be highly effective in 1–2-, ≤4-, and ≤16-year-olds.		
			Study type: NR (n=3) Data source: Surveillance/ hospital discharge data	No vaccination	Up to 7yrs after UVV introduction	Hospitalisation associated with varicella	Hospitalisation associated with varicella 65% decrease in hospitalisations from 13.3 to 4.8 per 100,000 people over a 6yr period since UVV introduced. 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. 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 % of varicella-related complications decreased in all age groups from 0.4% in 2005/2006 (first season of		

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							UVV) to 0.2% by 2008/2009 (fourth UVV season).		
		Italy: Two-dose monovalent, quadrivalent MMRV or both (regional implementation from 2005 and national implementation from 2017)	Study type: NR (n=3) Data source: Epidemiological database/analyses	No vaccination	Various including up to 9yrs after UVV introduction	Incidence of varicella	Incidence of varicella Pooled data from all 8 regions that had implemented regional UVV programs since 2003 showed a substantial reduction of varicella cases by 2012. 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. In Sicily, varicella notifications decreased by >95% between 2003 and 2012.		
			Study type: NR (n=3) Data source: Epidemiological database/analyses	No vaccination	Various	Hospitalisation associated with varicella	Hospitalisation associated with varicella 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. Pooled data from all 8 regions that had		

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
							implemented regional UVV programs since 2003 showed a substantial reduction of varicella-related hospitalisations by 2012. 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: Two-dose monovalent, quadrivalent or both (national implementation from 2009) From 2011, MMR+V vaccinations were recommended for the first dose instead of MMRV. Coverage: By 2015, coverage for the 1st dose was 80-90% and < 4% who got the 1st dose weren't getting the 2nd dose.	Surveillance studies (n=2) Others (study type NR) (n=5) Data sources: Surveillance/ sentinel data, hospital discharge data, health insurance claims, paediatric practice data	No vaccination and NA	Within 5yrs after UVV introduction	Vaccine effectiveness (VE) (and coverage) Incidence of varicella	Vaccine effectiveness (VE) 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. 1 study showed that 2-dose effectiveness for all combinations of varicella and MMRV vaccines 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. Incidence of varicella The overall picture indicates 3- to 4-fold decreases in the incidence of varicella infection with the introduction of the 2-		

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
							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) Data Source: Surveillance/health insurance claims	Interval between dose 1 and dose 2	NR	Vaccine effectiveness	Vaccine effectiveness 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 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 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) Data Source: Surveillance/health records and patient questionnaires	1-dose	NR	Incidence of breakthrough varicella	Incidence of BV 2 doses of vaccine were associated with a lower risk of breakthrough than a single dose.		

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
			Study type: NR (n=1) Data Source: National hospital discharge data	No vaccination	Within 3yrs after 2-dose UVV introduction	Hospitalisation associated with varicella	Hospitalisation associated with varicella 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.		
		Italy: 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 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;

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Marin[165] 2016 10.1542/peds.2015-3741 US CDC 1995 to 15 December 2014	Immunocompetent children aged 12mths to 18yrs. (Outcomes predominantly calculated among preschool and elementary school-aged children). 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 Varivax (n=23 studies) Varilrix (n=9) Unspecified (n=6) Multiple (n=6) Baike (n=1) Changsheng (n=1) Keygen (n=1) Okavax (n=1) Shanghai (n=1) *Some studies reported data on >1 named vaccine brand.	Total: 42 studies Retrospective cohort (n=29) Matched case-control (n=10) Prospective cohort (n=1) Time-series regression model (n=1) Household contact study (n=1)	NR	Varied; <10yrs is likely median time since vaccination	Vaccine Effectiveness (VE) for prevention of: all varicella‡ moderate/severe¥ varicella severe varicella varicella-related hospitalisation ‡ In measuring outcomes, 37/42 studies used clinically diagnosed varicella with details on illness obtained from parents; 5 studies used laboratory confirmed varicella. ¥In 18/30 studies, severity of disease was defined as mild, <50 lesions; moderate, 50-500 lesions; and severe, ≥500 lesions or a	Pooled VE (95% CI) for prevention of <u>all varicella</u> (random effects model) Overall (n=58 estimates): 81% (78 to 84%, I^2=88%) Varivax (n=26 estimates): 82% (79 to 85%, I^2=62%) Varilrix (n=10 estimates): 77% (62 to 85%, I^2=92%) Other vaccines (n=5 estimates): 86% (78 to 91%, I^2=39%) Mixed/multiple (n=17 estimates): 81% (76 to 85%, I^2=85%) Pooled VE (95% CI) for prevention of combined <u>moderate and severe varicella</u> (random effects model) Overall (n=34 estimates): 98% (97 to 99%, I^2=85%) Varivax (n=18 estimates): 98% (95 to 99%, I^2=86%) Varilrix (n=6 estimates): 98% (89 to 100%, I^2=79%) Other vaccines (n=1 estimate): 100% (91 to 100%, I^2=NR) Mixed/multiple (n=9 estimates): 99% (95 to 100%, I^2=86%)	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. 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 Not conducted Overall quality of evidence assessment 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
						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 lesions, number of days the patient needed rest and presence of complications, hospitalization only, or parental subjective assessment of severity.	No significant association between VE and vaccine type or study design. VE for prevention of <u>severe varicella</u> 100% (n=24 estimates) 85% (n=1 estimate for prevention of varicella-related hospitalisations).		

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 Priorix-Tetra (n=1 study)	Total: 1 study Retrospective cohort study (n=1)	NR	Unclear	VE for prevention of: all varicella severe varicella* *not clear what type of varicella diagnosis and what definition for varicella severity applies.	VE (95% CI) for prevention of <u>all varicella</u> Priorix-Tetra (n=1 estimate): 55% (8 to 78%) VE for prevention of <u>severe varicella</u> Priorix-Tetra (n=1 estimate): 100%		
		Two-dose monovalent Breakdown of vaccine brands not provided (n= 8 studies)	Total: 8 studies Cohort studies (n=4) Case-control studies (n=4)	NR	Unclear (5 years reported in 1 study)	VE for prevention of: all varicella* *not clear what type of varicella diagnosis applies.	Pooled VE (95% CI) for prevention of <u>all varicella</u> (random effects model) Overall (n=8 estimates): 92% (88 to 95%, I^2=57%)		
		Two-dose quadrivalent Priorix-Tetra (n=1 study)	Total: 1 study Cohort study (n=1)	NR	Unclear	VE for prevention of: all varicella* *not clear what type of varicella diagnosis applies.	VE (95% CI) for prevention of <u>all varicella</u> 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;

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Meszner[173] 2019 10.1080/14760584.2019.1573145 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA 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). Latvia (n=1 study)	One-dose quadrivalent MMRV Latvia (One-dose from 2008. Two-dose from 2019 but no data on impact of two-dose)	Total: 1 study Study type: not clear	NR	NR	Incidence of varicella Hospitalisation associated with varicella	Latvia Incidence of varicella 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. Hospitalisation associated with varicella 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. For countries that do not have UVV, introduction of UVV is predicted to provide substantial reductions in cases and rates of associated complications, with important economic benefits.	Risk of bias Not conducted Overall quality of evidence assessment Not conducted

Key: CEE – Central and Eastern Europe; EUVAC - European surveillance network for vaccine-preventable diseases; MMRV – measles, mumps, rubella, 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
New Zealand National Health Committee[174] 2012 DOI: NR; Link: https://www.moh.govt.nz/notebook/nbbooks.nsf/0/1BA074BCCABF911ACC257F7F000A4101/$file/nhc-varicella-vaccine-assessment-report.pdf Funding: Review conducted by an independent statutory authority 1 January 2009 to 16 September 2011 (HTA Agency & repositories); to 2 November	Children aged 0-5yrs	One-dose (vaccine type NR)	Total for overall VE: 17 studies including case control, cohort (outbreak) and house contact studies. Germany: n=1 study Analysis of sentinel dataset	No vaccination	NR	Vaccine effectiveness against varicella (any severity) Vaccine effectiveness against varicella (moderate/severe)	Vaccine effectiveness VE against all varicella: 81% VE against moderate and severe varicella combined: 97% VE against severe varicella: 100% <u>Germany</u> 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 Not conducted Overall quality of evidence assessment Not conducted
			Total: 5 studies Study type NR 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 <u>USA</u> Since the implementation of the 1-dose vaccination program in 1995, varicella related hospitalisation numbers and rates declined significantly. 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.		

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
2011 (MEDLINE & Cochrane and 16 November 2011 (EMBASE)							<u>Australia</u> 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. <u>Germany</u> 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. 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 1-4yrs old (from >20 hospitalised varicella cases per 100,000 population in 1994-2004 to 10 in 2007) and in infants (from >30		

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
							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 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Pallas[163] 2011 <u>Not published</u> 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	Human subjects vaccinated with VZV vaccine	At least one-dose monovalent or quadrivalent MMRV (multiple brands)	Total: 7 studies SR (n=3 ->15 unique studies including 9 RCTs and 6 observational studies); RCT (n=1); Other (n=3);	No vaccination or placebo	Up to 7yrs; 9mths	Vaccine effectiveness (VE) against varicella (any severity) Vaccine effectiveness (VE) against varicella (moderate/severe)	Vaccine effectiveness Overall, varicella vaccination appears to be effective, with VE rates around ≥80%. VEs for preventing moderate/severe disease (measured in 4 studies) was between 97% and 100%. 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 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. Overall quality of evidence assessment No overall quality of
		At least one-dose monovalent or quadrivalent MMRV (multiple brands)	Total: 9 studies SR (n=3); MA (n=1 ->15 unique studies; Other (n=5);	No vaccination	NR	Vaccine effectiveness (VE) in outbreak settings (schools and child care centres)	Vaccine effectiveness in outbreak settings VE for varicella vaccination in outbreak settings ranged between 20% and 93%. VE for moderate/severe disease appears to be high for all vaccine types in any outbreak setting. 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	Total: 17 studies	No vaccination	4-10yrs (incidence)	Incidence of varicella	Incidence of varicella (n=9 studies)		

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
additional study is added here. PubMed: 1 September 1995 to 1 September 2010 Embase: 1995 to 2011 Cochrane Library: 2000 to 2010		quadrivalent MMRV	Surveillance (n=8); Multiple cross-sectional (n=1); Retrospective (n=4); NR (n=4)		5-15yrs after vaccine introduction (hospitalisation)	Incidence of breakthrough varicella (BV) Hospitalisation associated with varicella Complications associated with varicella Mortality associated with varicella	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. Hospitalisation associated with varicella (n= 8 studies) After vaccine introduction or compared to pre-vaccination status, varicella-related hospitalisations significantly declined by 43%-88% for all age groups, over a period of 5-15 years. No change was observed in the mean duration of hospital stay. Complications associated with varicella (n=4 studies) After the introduction of varicella vaccination, the occurrence of varicella-related complications significantly decreased.		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).

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
							Mortality associated with varicella (n=1 study) During the 12yrs 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 Surveillance (n=6); Prospective cohort (n=1)	NA	NR	Proportion of BV	Proportion of BV (n=3 studies) 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 Study type: various	Age at vaccination	NR	Incidence of BV	Incidence of BV Younger age at vaccination (≤14-18 months) may be a risk factor for vaccine failure, but the evidence was not consistent. Children vaccinated at an age of ≤2yrs may be at lower risk for moderate/severe BV compared with children vaccinated at an older age.		

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
				Time since vaccination	Up to 10yrs		Incidence of BV Mild BV rates do not seem to increase over time since immunisation (<10 years) in children at risk of exposure. A few studies reported significant higher risk ratios for children vaccinated >5yrs ago compared to children immunised more recently. Evidence indicates that if BV occurs, moderate/severe cases are more often observed with increasing time since immunisation.		
			Total: 3 studies Study type: various	Co-administration with another vaccine (MMR)	NR		Incidence of BV 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Skull[162] 2001 10.1136/adc.85.2.83 Funding: NR 1966 to December 2000	Human subjects vaccinated with VZV vaccine	One-dose (vaccine type NR)	Total: 21 studies RCTs (n=6) Prospective cohort (n=14) Post-licensure study (n=1)	Placebo and no vaccination	Up to 7yrs (1 RCT)	Vaccine effectiveness against varicella Long-term persistence of protection against varicella Attack rate Risk of breakthrough varicella	Vaccine efficacy/ effectiveness 2 RCTs provide evidence that a single dose of VZV vaccine for children (aged 10mths to 14yrs) is effective in preventing varicella as follows: VE: 100% over 9mths and 98% over 7yrs (data beyond 3yrs subject to large loss to follow-up) (1 RCT) VE: 72% over a mean of 29mths (1 RCT) Attack rates in both RCTs were 0-3% per year in vaccinated group versus 7-11% in placebo group. A cohort study of vaccinated and unvaccinated children <5yrs old found a VE of 83%. Supporting evidence for vaccine effectiveness is provided by 3 more RCTs and 12 prospective cohort studies. 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.	This critical review has found strong evidence for the effectiveness of VZV vaccination in the prevention of varicella in children.	Risk of bias Studies were systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care. The results for individual studies are not provided. The quality of evidence in studies included in this analysis was reported as generally good. However, the following methodological issues were identified. Loss of subjects from analysis was sometimes considerable, particularly where the duration of follow up was ≥7yrs. Other

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
							Supportive evidence of a low annual attack rate in vaccinees (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%). 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.		trials relied on self-reporting of VZV disease to investigators, while occasional studies followed only vaccinees who initially seroconverted. These biases could potentially result in an over estimation of VE by underestimatin g the true number of cases. However, outcomes across studies were consistent regardless of study design or duration of follow up, suggesting a true effect. Overall quality of evidence assessment Using the Canadian Task Force on Preventive Health Care methodology, there was

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
									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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Xu[169] 2019 10.13200/j.cnki.cjb.002616 http://www.cqvip.com/qk/97789x/20195/7002176336.html Funding source not provided Period before 2017	Children and students in varicella outbreak clusters in China	One-dose (vaccine type NR)	Total: 3 studies Study type: unclear	No vaccination	NR	Vaccine effectiveness for prevention of varicella	Pooled VE against varicella (95% CI) (random effects model) 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 Not conducted Overall quality of evidence assessment Not conducted
	Children and students in varicella outbreak clusters in China	Two-dose (vaccine type NR)	Total: 3 studies Study type: unclear	No vaccination	NR	Vaccine effectiveness for prevention of varicella	Pooled VE against varicella (95% CI) (random effects model) Overall (n=3 estimates): VE 92% (80 to 97%, I^2=0%)¥ ¥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 Case-control (n=19) Cohort (n=15)	No vaccination	NR	Vaccine effectiveness for prevention of varicella	Pooled VE against varicella (95% CI) (random effects model) Overall (n=34 estimates): VE 69% (64 to 73%, I^2=69%) <u>By study design</u> Case-control (n=19 estimates): VE 68% (61 to 74%, I^2=72%) Cohort (n=14 estimates): VE 71% (63 to 77%, I^2=65%) <u>By school</u> Preschool (n= 2 estimates): VE 78% (60 to 87%, I^2=0%)‡ Primary school (n=2 estimates): VE 33% (4 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
						Long-term persistence of protection based on incidence of breakthrough varicella over time	‡Difference in VE between preschool and primary school children statistically significant (p<0.00001) <u>By current age (recommendation is vaccination once 12mths old)</u> Overall (n=12 estimates): VE 79% (63 to 88%, I^2=89%) <5yrs old (n=3 estimates): VE 94% (69 to 99%, I^2=91%) <9yrs old (n=4 estimates): VE 87% (64 to 96%, I^2=88%) ≥9yrs old (n=5 estimates): VE 41% (23 to 54%, I^2=0%) 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Yin[160] 2018 doi.org/10.1080/14760584.2018.1433999 Natural Science Foundation of Guangdong Province, China 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 RCT (n=2)	One-dose	3-10yrs	Incremental vaccine efficacy (VE) against varicella‡ ‡defined in this review as clinical and/or laboratory-confirmed	Pooled incremental VE (95% CI) against <u>any severity varicella</u> (random effects model) Overall (n=2 estimates): 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 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. Overall quality of
	Immunocompetent children (n=2,389) aged 12mths to 13yrs at day-care centres or schools that experienced outbreaks in America, Spain, China, and Germany	Two-dose (vaccine type NR) (coverage 10-67%)	Total: 7 studies 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) Overall (n=8 estimates): VE 63% (36 to 79%, I^2=54.6%)		
		Two-dose (vaccine type NR) (coverage 39-67%)	Total: 2 studies 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) Overall (n=3 estimates): VE 42% (-0.01 to 67%, I^2=59.5%)		
		Two-dose (vaccine type NR) (coverage 10-65%)	Total: 5 studies 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) Overall (n=5 estimates): VE 80% (62 to 90%, I^2=0%)		
	Immunocompetent children (n=1,547) aged 15mths to 18.7yrs in Connecticut (USA), West	Two-dose (vaccine type NR)	Total: 5 studies 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) Overall (n=6 estimates): VE 81% (65 to 90%, I^2=26.4%)		

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
	Virginia (USA), Spain, Germany, Antelope Valley (USA), Canada, Philadelphia, and Panama								evidence assessment Not conducted

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Zhang[167] 2020 10.3760/cma.j.cn112338-20191025-00762 Funding source not reported Period before 2019	Healthy children (n=328,565) aged 1-12yrs in China	One-dose (vaccine type NR)	Total: 32 studies Retrospective Cohort (n=20) Prospective Cohort (n=6) Case-control (n=6)	No vaccination	NR	Vaccine effectiveness for prevention of varicella	Pooled VE against varicella (95% CI) (random effects model) Overall (n=32 estimates): VE 75% (68 to 80%, I^2=83%) <u>By study design</u> Cohort (n=26 estimates, n=323,123 children): VE 72% (65 to 80%, I^2=84%) Case-control (n=6 estimates, n=5,433 children): VE 78% (67 to 85%, I^2=78%) <u>By setting</u> Outbreak (n=22 estimates, n=17,154 children): VE 66% (57 to 73%, I^2=62%) Non-outbreak (n=10 estimates, n=311,411 children): VE 85% (78 to 89%, I^2=87%) <u>By age of study participants</u> <6yrs old (n=12 estimates, n=8,124 children): VE 84% (77 to 89%, I^2=59%) ≥6yrs old (n=19 estimates, n=16,488 children): VE 60% (51 to 68%, I^2=55%) <u>By NOS quality score</u> ≥5 (n=20 estimates, n=19,890 children): VE 74% (71 to 77%, I^2=78%) <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 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. Overall quality of evidence assessment 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Zhang[158] 2021 10.1186/s12879-021-06217-1 Beijing Natural Science Foundation, China 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 Retrospective cohort (n=11) Prospective cohort (n=1)	No vaccination	Unknown	Vaccine effectiveness (VE) against varicella	Overall pooled VE (95% CI) against varicella (random effects model) Overall (n=12 estimates): 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 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. Overall quality of evidence assessment GRADE quality of evidence assessment was undertaken. Overall, the evidence quality assessment of the pooled two-dose VE was LOW. The quality of evidence assessment of the pooled VE of
	Healthy children (n=83,560) aged 2-12yrs in China in a non-outbreak community setting (n=2 studies)		Total: 2 Retrospective cohort (n=1) 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> (fixed effects model) Overall (n=2 estimates): 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 Retrospective cohort (n=10)			Vaccine effectiveness (VE) against varicella in outbreak settings	Pooled VE (95% CI) against varicella <u>in outbreak settings</u> (fixed effects model) Overall (n=10 estimates): VE 87% (76 to 93%, I^2=0%)		
	Healthy children (n=86,367) aged 2-12yrs in China in the following settings:		Total: 9 studies scoring ≥7 on NOS Retrospective cohort (n=9)			Vaccine effectiveness (VE) against varicella	Pooled VE (95% CI) against varicella <u>for studies scoring ≥7 on NOS</u> (random effects model) Overall (n=9 estimates): 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
	Elementary school (n=7 studies), Kindergarten and elementary school (n=1), Community (n=1)								subgroups with an NOS score ≥7 was assessed as MODERATE. It was assessed as LOW in subgroups with an NOS score <7.
	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 Retrospective cohort (n=2) Prospective cohort (n=1)			Vaccine effectiveness (VE) against varicella	Pooled VE (95% CI) against varicella for studies scoring <7 on NOS (fixed effects model) Overall (n=3 estimates): VE 88% (71 to 95%, I^2=0%)		

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Zhu[168] 2017 10.16506/j.1009-6639.2017.08.008 Hangzhou Municipal Health Science and Technology Program Project (2016B46) 1998 to March 2016	Children (n=421,189) aged 0-18yrs in China Community, kindergarten, primary school, junior high school, secondary school, and rehabilitation centre settings	One-dose (vaccine type NR)	Total: 35 studies Cohort (n=6) Case-control (n=28) Cross-sectional (n=1)	No vaccination	NR	Vaccine effectiveness for prevention of varicella	Pooled VE against varicella (95% CI) (random effects model) Overall (n=35 estimates): VE 75% (68 to 80%, I^2=90.7%) <u>By study type</u> Cohort (n=6 estimates, n=300,608 children): VE 88% (82 to 92%, I^2=NR) Case-control (n=28 estimates, n=119,443 children): VE 67% (59 to 73%, I^2=NR) <u>By schooling status</u> Pre-school/≤6yrs (n=10 estimates, n=61,256 children): VE 90% (81 to 95%, I^2=NR) Primary school (n=17 estimates, n=11,574 children): VE 67% (52 to 78%, I^2=NR) <u>By vaccine</u> Imported (n=6 estimates, n=16,146 children): VE 75% (63 to 83%, I^2=NR) Domestic (n=10 estimates, n=275,901 children): VE 79% (71 to 85%, I^2=NR) <u>By setting</u> 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 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. Overall quality of evidence assessment 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Efficacy/ effectiveness outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Zhu[161] 2018 10.1016/j.ajic.2017.07.029 Funding source NR (No start date reported) 30 September 2016	n=27,618 breakthrough varicella cases in healthy children aged 9mths to 17yrs from studies in the following countries: Canada (n=1 study); China (n=2); Germany, Belgium & Netherlands (n=1); Israel (n=1); Italy (n=1); Japan (n=2); Singapore (n=1); Taiwan (n=2); Turkey (n=1); USA (n=12)	One-dose monovalent or quadrivalent MMRV (various vaccines) Varivax (n=11); Varilrix (n=4); Okavax (n=2 studies); Not available (n=2); MMRV (n=1); MMR II and Varivax (n=1); Oka strain (n=1); Varivax and Varilrix (n=1); Changchun (n=1);	Total: 24 studies (30 study populations) RCT (n=4) Prospective cohort (n=17) Retrospective cohort (n=2) 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) (random effects model, unless otherwise stated) Overall: 8.5 (5.3 to 13.7, I^2=99.8%) By vaccine type Varivax (n=14 study populations): 13.9 (11.1 to 17.4, I^2=96%) Varilrix (n=4 study populations): 28.2 (13.7 to 58.0, I^2=98.9%) Other monovalent: (n=3 study populations): 3.2 (1.5 to 7.0, I^2=99.5%) Quadrivalent MMRV (n=3 study populations): 3.2 (0.7 to 15.4, I^2=77.1%) By study design RCT (n=4 study populations, fixed effects model) 6.5 (4.5 to 9.4, I^2=0%) Prospective cohort (n=17 study populations): 14.9 (10.5 to 21.1, I^2=98.8%) Retrospective cohort (n=2 study populations): 41.1 (18.7 to 90.4, I^2=97.7%) Computer based/system studies (n= 7 study	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 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. Summary: 20% scored 4, 63% scored 5, and 17% scored 6. Overall quality of evidence assessment 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
							populations): 1.7 (0.93 to 3.0, I^2=99.4%) By region Asia (n=12 study populations): 5.1 (2.4 to 10.9, I^2=99.8%) North America (n=15 study populations): 15.5 (12.1 to 19.8, I^2=96.9%) Europe (n=3 study populations): 3.2 (0.7 to 15.4, I^2=77.1%) By age at vaccination ≤2yrs (n=13 study populations): 4.7 (2.2 to 9.8, I^2=99.9%) >2yrs (n=6 study populations): 18.7 (10.7 to 32.8, I^2=98.1%) Mixed age (n=11 study populations): 10.6 (4.7 to 23.9, I^2=99.5%) By NOS score NOS = 4 (n=6 study populations): 15.8 (9 to 27.5, I^2=98.2%) NOS=5 (n= 19 study populations): 5.5 PY (3 to 10.1, I^2=99.8%) NOS=6 (n=5 study populations): 18.7 PY (12.6 to 27.6, I^2=83.6%) 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		

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
							approximately 71.74% of the heterogeneity. Pooled annual BV incidence rate. Cases per 1,000 person years (95% CI) By time since vaccination 1st yr after (n=14 study populations): 13.2 (7.2 to 24.08, I^2=96.4%) 2nd yr after (n=12 study populations): 28.0 (1.6 to 53.7, I^2=95.1%) 3rd yr after: (n=9 study populations): 15.0 (5.8 to 39.1, I^2=94.6%) 4th yr after: (n=10 study populations): 35.3 (17.6 to 71.1, I^2=93.2) 5th yr after: (n=7 study populations): 23.7 (7.3 to 77.5, I^2=96.8) 6th yr after: (n=6 study populations): 24.7 (5.1 to 119.5, I^2=97.5) 7th yr after: (n=4 study populations): 10.5 (0.4 to 266.4, I^2=97.9%) 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); MMR+Varilrix (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) 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); Germany, Belgium & Netherlands (n=1); USA (n=2)	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 A 2.4 Results from reviews that assessed 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,[160, 161] with a further review providing a narrative synthesis of findings.[175] A summary of the characteristics of reviews that included two- versus one-dose vaccination is provided in Table A 2.4. A narrative summary of results by outcome and vaccine type is provided below.

Outcome: Efficacy/effectiveness in preventing varicella

Monovalent or quadrivalent vaccine (vaccine type unclear)

A single review specifically examined incremental VE, defined as the additional reduction in varicella disease experienced by two-dose vaccine recipients, relative to one-dose recipients, and conducted a meta-analysis.[160] 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).[160] In outbreak settings (day care centres and schools) pooled incremental VE was 63% (95% CI: 36 to 79%, I^2=54.6%; n=2,389, 7 retrospective cohort studies).[160]

Outcome: Incidence of breakthrough varicella

Monovalent and quadrivalent vaccine (vaccine type unclear)

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).[161] 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).[161] 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.[175]

Table A 2.4 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[175]	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[160]	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[161]	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.

Appendix A 2.5 Results from reviews that assessed any-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,[159, 169] with three further reviews providing a narrative synthesis of findings.[88, 163, 175] 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[169] and the three reviews that provided a narrative synthesis of findings.[88, 163, 175] 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 E1, with a narrative summary of results by outcome and vaccine type provided below.

Outcome: 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.[159]

Quadrivalent MMRV vaccine

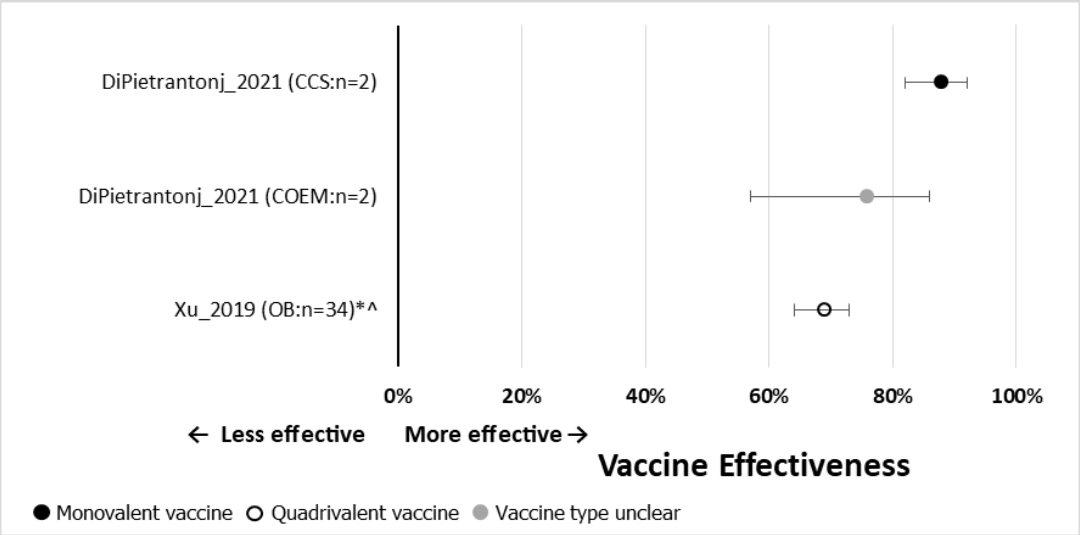
A single review reported pooled vaccine effectiveness of any-dose of quadrivalent vaccine against varicella of 76% (95% CI: 57 to 86%; I^2=100%; 2 case-only ecological method studies).[159] The same review reported vaccine effectiveness of any-dose of the quadrivalent vaccine (Priorix-Tetra®) of 86% (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.[159]

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.[163, 169, 175] 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).[169] 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]) ($p<0.00001$).[169] 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.[169] 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).[163] 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.[175] 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.[163]

Figure A 2.5 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 A 2.5 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).

Outcome: 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.[163] 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.[175]

Outcome: 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.[159]

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).[163] 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.[175]

Outcome: 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).[88] 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.[163] 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.[163] The review also reported that evidence indicates that if BV occurs, moderate or severe cases are more often observed with increasing time since immunisation.[163] 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.[163]

Table A 2.5 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[159]	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	VE 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[175]	Healthy children aged 1-12yrs at vaccination	NR	NR	Various	VE 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 possibility of two doses may be considered.	×	✓	Critically Low
Kaufmann 2020[88]	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 Germany: various including up to 10yrs post vaccination	Italy: Incidence of varicella; Hospitalisation and complications associated with varicella Germany: VE 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. Further reductions were reported in Italy and Germany after the recommendation of a 2nd dose in a long or short schedule, respectively.	✓	×	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
Pallas 2012[163]	Human subjects vaccinated with VZV vaccine	NR	NR except MMR for risk of breakthrough varicella	Various incl. NR 4-10yrs (incidence) 5-15yrs (hospitalisation)	VE against varicella; Incidence of (breakthrough) varicella; Hospitalisation and complications associated with varicella; 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 2019[169]‡	Children and students in varicella clusters/outbreaks in China	NR	NR	NR	VE against varicella	Meta-analysis	Varicella immunisation has a certain protective effect, which decreases with increasing vaccination age.	×	×	Critically 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; VE – vaccine effectiveness; VZV – varicella zoster vaccination;

Appendix A 2.6 AMSTAR2 Quality Appraisal

Review	AMSTAR 2 Questions																	
	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 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_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_2021	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_2020	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

Review	AMSTAR 2 Questions																	
	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 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?	
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; NA – not applicable; NRSI – non-randomised study of intervention; RCT – randomised controlled trial.

Supplementary Appendix for Chapter 3

Appendix A 3.1 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) 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*) 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)" Search limited to 1,000 hits per website and filetype 'pdf'.		1,000

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 Health 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

Country	Name of Agency/Unit/Ministry	Website domain
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	Mnistry 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
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

Country	Name of Agency/Unit/Ministry	Website domain
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
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

Country	Name of Agency/Unit/Ministry	Website domain
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
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

Country	Name of Agency/Unit/Ministry	Website domain
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 Clincal 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

Country	Name of Agency/Unit/Ministry	Website domain
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 A 3.2 Excluded studies retrieved from databases, registries and grey literature sources

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	Not a systematic review
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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	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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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
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

Study number	Title	Authors	Year Published	DOI/ Weblink	Exclusion reason
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 A 3.3 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Amaral[191] 2021 10.1111/jpc.15303 Funding source: NR From (start date not reported) to 1 June 2020	Cases of varicella reactivation meningitis post varicella vaccination in immunocompetent children Mean age (±SD) when first vaccinated = 1.4yrs (±0.7)	**At least one-dose monovalent or quadrivalent MMRV,** **One-dose (n=8 studies)** **Two-dose (n=1)**	Total: 9 studies (study design not reported)	NA	Up to 10yrs in 1 study (two-dose schedule) Mean interval between vaccination and reactivation (± SD) = 5.6yrs (± 2.9)	Safety - varicella reactivation meningitis	**Safety - varicella reactivation meningitis** • 9 cases of varicella reactivation meningitis post varicella vaccination, in immunocompetent children reported • Mean age (± SD) at presentation of VZV meningitis = 7yrs (±3.4) • Of these 9 cases, clinical data were presented for 8. Clinical presentation, n/N (%): ○ headache 8/8 (100) ○ vomiting 4/8 (50) ○ fever 6/8 (75) ○ rash 8/8 (100) ○ photophobia 2/8 (25) • Meningism in neurological exam, n/N (%): 5/8 (63) • Resolution data presented for all 9 cases: ○ full recovery without neurological	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** Not conducted **Overall quality of evidence assessment** 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
							sequelae n/N (%) 9/9 (100%).		

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Bauwens[184] 2019 10.3390/vaccines8010012 No external funding received 1999 to 28 January 2019	Paediatric population under 18yrs of age Canada (n=1 study); Finland (n=1); Germany (n=1); Germany & Italy (n=1); Italy (n=1); Philippines (n=2); USA (n=3);	**VAR+MMR+Hib-HepB co-administration** (Dosage NR)	Total: 1 study RCT (n=1) n=822 children aged 12-15mths	VAR+MMR+Hib -HepB separate administration	NR	Safety (rash and rhinorrhea)	**Safety – rash and rhinorrhea** • Significantly less rash (RD: -5.8%, RR: 0.6) and less rhinorrhea (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** Not conducted **Overall quality of evidence assessment** Not conducted
		MMRV+PCV7 co-administration (Dosage NR)	Total: 1 study RCT (n=1) n=1027 children aged 12-15mths	MMRV+PCV7 separate administration	NR	Safety (nasopharyngitis and insomnia)	**Safety – nasopharyngitis and insomnia** • 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 RCT (n=3) n=2,514 children aged 12-24mths	MMR + VAR separate administration	NR	Safety (adverse events)	**Safety – adverse events** • No statistically significant difference in adverse events (not specified) between groups following immunisation.		
		MMRV + DTaP + Hib-HepB co-administration (Dosage NR)	Total: 1 study RCT (n=1) 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 RCT (n=2) 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	Total: 1 study Case control (n=1) n=590 children aged 16-23mths	MMRV or MMR + DTaP-IPV/Hib or DTaP-HepB-IPV/Hib separate					

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)		administration					
		MMRV + MenACWY co-administration (Dosage NR)	Total: 1 study RCT (n=1) n=100 children aged 12-23mths	MMRV + MenACWY separate administration					
		MMRV + MenC co-administration (Dosage NR)	Total: 1 study RCT (n=1) n=716 children aged 13-15mths	MMRV + MenC separate administration					

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Benchimol[176] 2021 10.1093/jcag/gwab015 and 10.1053/j.gastro.2020.12.079 Guideline was funded by the Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes, and CANImmunize. Lead author supported by a New Investigator Award from the Canadian Institutes of Health Research, Crohn's and Colitis Canada, and CAG. He	Varicella-susceptible paediatric patients with IBD not on immunosuppressive therapy with the associated systematic review based on the general population (see below) (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** (vaccine type not reported)	Total: 2 studies Systematic reviews (SR): n=2 (1 SR includes a further 2 SRs) Safety outcome: 7 RCTs and 5 observational studies	No vaccination	NR	Safety of varicella vaccine (serious adverse events)	**Safety (serious adverse events)** 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** Cochrane RoB for RCTs and ROBINS-I for non-randomised studies Assessment for individual studies not provided. Overall deemed 'not serious' for safety studies relating to serious adverse events in healthy children in the general population. **Overall quality of evidence assessment** Safety The CoE of evidence for safety was anchored to the general

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
was also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program. 1989 to 12 April 2019									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.

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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Di Pietrantonj[159] 2021 10.1002/14651858.CD004407.pub5 National Institute for Health Research (NIHR) via the NIHR Cochrane Incentive Award Scheme 2018 - 128383 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 **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)** (random effects model) • 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** Risk of bias conducted for all primary studies. Case-control (prospective and retrospective) and cohort studies assessed using the appropriate Newcastle-Ottawa Scales. Case-only ecological method studies, self-controlled case series and person time cohort studies assessed for *case selection, exposure,*
	n=180,480 children aged up to 15yrs	**Quadrivalent MMRV**	Total: 2 studies **Self-controlled case series/ person time cohort** (n=2)				**Pooled rr for seizures (95% CI)** (random effects model) • 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** Priorix-Tetra and ProQuad	Total: 5 studies **Cohort study** (n=5)	MMR (no varicella vaccine)	0-42 days after vaccination	Safety: Seizures (febrile/afebrile)	**Pooled RR for seizures (95% CI)** (fixed effects model) • Overall (n=6 estimates): 1.53 (1.37 to 1.71, I^2=71%) • Priorix-Tetra (n=3 estimates from 2 studies): 1.28 (1.00 to 1.64, I^2=0%) • 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** Priorix-Tetra and ProQuad	Total: 6 studies **Cohort study** (n=6)	MMR (no varicella vaccine)	7-10 days after vaccination	Safety: Seizures (febrile/afebrile)	**Pooled RR for seizures (95% CI)** (fixed effects model) • Overall (n=7 estimates): 1.50 (1.36 to 1.66, I^2=81%) • Priorix-Tetra (n=3 estimates from 2 studies): 2.49 (1.66 to 3.74, I^2=0%) • 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)** • Overall (n=1 estimate): 2.87 (0.78 to 10.56)		*observation and exposure risk period and comparability*. Safety studies 9/9 (100%) varicella studies rated as 'low' risk of bias. **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**
Author Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Garrido[175] 2012 10.32385/rpmgf.v28i2.10928 No funding received January 2005 to November 2009	Healthy children aged 1-12yrs at vaccination 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 Systematic reviews (SRs) (n=3); Meta-analysis (n=1); Primary studies (n=7)	No vaccination or placebo	NR	Safety (serious adverse events) Safety (short term effects of vaccination)	**Vaccine safety** • 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. • 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** Not conducted **Overall quality of evidence assessment** The Strength of Recommendation Taxonomy (SORT) scale from the American Family Physician Foundation was used. 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).
		At least one dose (vaccine type not reported)		No vaccination		Safety (short term effects of vaccination) Safety (adverse events) Safety (death)	**Vaccine safety** • 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		

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
							of complications were recorded: conjunctivitis in an unvaccinated child and bacterial infection of the skin in a vaccinated child. • 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 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		The remaining studies were not graded.

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
							adverse effects, so the benefits conferred outweigh the potential risks. • 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 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Gidengil[182] (Agency for Healthcare Research and Quality - AHRQ) 2021 (this is an update of 2014 AHRQ report, which itself built upon the 2011 Institute of Medicine (IOM) consensus report)‡ 10.23970/AHRQEPCCER244 10.1016/j.vaccine.2021.03.079 (linked publication) Funded under Contract No. HHSA290201600010I from the AHRQ, U.S.	Children (11-23mths) for whom vaccines for routine immunisation in the United States are recommended	**Monovalent Varivax and unspecified brand** (Dosage NR)	n=4 studies on monovalent varicella vaccine identified for 2021 update Study type: Cohort (n=1); Case-control (n=1); Self-controlled risk interval analysis (n=1); Other (n=2)	Active and inactive comparators Age at vaccination (seizures)	Various – including up to 9mths	Safety – various outcomes including anaphylaxis, 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** • Causal relationship between varicella vaccine and: ○ anaphylaxis ○ disseminated Oka strain of VZV without other organ involvement (not examined as key adverse events in current report) ○ vaccine strain viral reactivation without other organ involvement (herpes zoster) ○ vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis, all based on mechanistic evidence: HIGH Strength of Evidence (SoE) **Findings in 2021 update** • Insufficient evidence for the following outcomes: ○ acute disseminated encephalomyelitis (1 study of children and adults reported no systematic increased risk [aOR 4.3; 95% CI 0.5, 25.4]	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** Conducted using the McHarm Quality Assessment Scale for adverse events **Overall quality of evidence assessment** 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

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
Department of Health and Human Services (HHS). At least 2011 to November 2020 ‡ 'Summary of main findings' over includes summary from 2014 AHRQ report, new studies identified since 2014 and summary from 2021 AHRQ report.							○ 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) ○ optic neuritis (1 study of children and adults detected no systematic increased risk [aOR 2.1; 95% CI 0.1 to 23.2]) ○ 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 15mths to 3.64 (95% CI 1.86 to 7.12) when administered at 16 to 23mths of age). ○ sudden sensorineural hearing loss (1 study reported no association within 1 week of vaccination) ○ transverse myelitis (1 study of children and adults reported no increased risk		and (iv) reporting bias. 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
							[aOR 0; 95% CI 0.00 to 10.7]) ○ 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). • No studies identified reporting on the following outcomes: ○ anaphylaxis or systemic allergic reaction ○ angioedema ○ ataxia ○ cardiovascular events ○ death ○ diabetes ○ encephalitis/ encephalopathy ○ Guillain-Barré syndrome ○ herpes zoster ○ idiopathic thrombocytopenic purpura ○ meningitis ○ secondary transmission of live varicella virus ○ stroke. **Summary - 2021 AHRQ Vaccine Safety Report** (no change from 2014 Report)		

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
							• High Strength of Evidence (SoE) of increased risk of the following adverse events (causal relationship based on mechanistic evidence): ○ 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. Estimates of the magnitude of increased risk was not determined. • Insufficient SoE of increased risk of the following adverse events: ○ seizures ○ acute disseminated encephalomyelitis ○ transverse myelitis ○ Guillain-Barré syndrome ○ small fibre neuropathy ○ onset or exacerbation of arthropathy and thrombocytopenia as new evidence was either graded as insufficient, there were no studies, or the outcome was not included as		

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
							a key adverse event.		
		Quadrivalent MMRV (ProQuad) (Dosage unclear)	Total: n=5/6 studies identified on quadrivalent MMRV vaccine for 2021 update Study type: RCT (n=1); Cohort (n=2); Self-controlled risk interval analysis (n=1) Other (n=2)	Active and inactive comparators Concomitant administration with another vaccine (febrile seizures) Age at vaccination (seizures)	Unclear	Safety – various outcomes including encephalitis/ encephalopathy, death, anaphylaxis, ataxia, febrile seizures, idiopathic thrombocytopenic purpura, Kawasaki disease, meningitis, seizures	**Summary - 2014 AHRQ Vaccine Safety Report** • No findings **Findings in 2021 update** • Low SoE for no increased risk for the following outcomes: 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]). o death (1 RCT; RR 0.50; 95% CI 0.01 to 25.33 [Number of events: 0/474 vs 0/239]). • Insufficient evidence for the following outcomes: 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. o ataxia (1 cohort study reported no increased risk) o febrile seizures (1 RCT comparing MMRV with a hexavalent vaccine to hexavalent vaccine alone identified 2 participants		

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
							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 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). ○ idiopathic thrombocytopenic purpura (1 cohort study reported an increased risk for some time intervals [RR 11.28; 95% CI 1.87 to 68.2]). ○ Kawasaki disease (1 cohort study reported no increased risk) ○ meningitis (1 cohort study reported no increased risk of meningitis/encephalitis (combined outcome) ○ 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		

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
							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-centred 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] 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. ○ 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		

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
							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]). • No studies identified reporting on the following outcomes: o angioedema o autism o cardiovascular events o diabetes o encephalitis/ encephalopathy o Guillain-Barré syndrome o herpes zoster o multiple sclerosis o secondary transmission of live varicella virus o stroke o transverse myelitis. **Summary - 2021 AHRQ Vaccine Safety Report** • LOW SoE of increased risk of the following outcomes: o acute disseminated encephalomyelitis		

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
							○ 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Grazina[189] 2020 10.7416/ai.2020.2333 Not funded 1 January 2000 - February 2018	Vaccinated individuals who developed Stevens-Johnson Syndrome (SJS) Included study: 27mth old baby	**Varicella vaccine**	Total: 1 study Case report and review (n=1)	NA	NR	Safety: Development of Stevens-Johnson Syndrome after vaccination	**Safety - Stevens-Johnson Syndrome** • 1 case of SJS following the administration of varicella vaccine, in a 27mth old baby (not reported whether the infant was immunocompetent or not). • 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. • 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** 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. **Overall quality of evidence assessment** 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Ma[183] 2015_a 10.1097/MD.0000000000000172 1 No funding received Earliest date available to 9 September 2014	Healthy children aged 0 to 6yrs	**1-dose quadrivalent MMRV Priorix-Tetra (GSK)**	Total: 6 studies RCT (n=6)	MMR	Within 4 days (0-3 days) after vaccination	Safety - solicited local symptoms: pain, redness and swelling	**Safety (pain, redness, swelling)** • 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): ○ Pain (any): RR 1.12 (0.95 to 1.32, I^2=0%) ○ Pain (Grade 3): RR 0.94 (0.21 to 4.13, I^2=0%) ○ Redness (any): RR 1.08 (0.96 to 1.22, I^2=24%) ○ Redness (Grade 3): RR 1.18 (0.50 to 2.79, I^2=0%) ○ Swelling (any): RR 1.22 (0.96 to 1.55, I^2=0%) ○ Swelling (Grade 3): RR 5.89 (0.72 to 48.16, I^2=0%) • Redness most frequently reported, 18.45% for MMRV group and 16.21% for MMR group. • Incidences of pain and swelling were around and below 10% in both groups, respectively.	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** Conducted using Jadad scale scoring from 0 (very poor quality) to 5 (rigorous). 8 RCTs scored 2; 2 RCTs scored 3 **Overall quality of evidence assessment** 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
							• Grade 3 local reactions were rare (<0.5%) for both groups, especially pain.		
			Total: 5 studies RCT (n=5)		Within 43 days (0-42 days) after vaccination	Safety - solicited general symptoms: fever	**Safety (fever)** • 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 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. • Pooled incidence of grade >39.5^{o}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). • 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)	Safety - solicited general symptoms: rash	**Safety (rash)** • Both incidences of measles/rubella-like rash and		

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
					after vaccination		varicella-like rash were significantly higher in MMRV groups than those in MMR groups. Pooled RR (95% CI, I^2) (fixed effects model: ○ RR measles/rubella-like rash: 1.45 (1.06 to 1.98, I^2=0%, p=0.020) ○ 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)** • 15 unsolicited adverse events (whether or not considered related to the vaccination studied) were analysed. • Incidence of pharyngitis was statistically higher in MMRV group compared to the MMR group. Pooled RR (95% CI, I^2) (fixed effects model: ○ 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)** • 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. • Approximately 50% of the related SAEs (n=2 studies) were febrile seizures. • The incidence of related febrile seizure was <0.8% in MMRV groups and <0.5% in		

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
							MMR groups. No statistical difference was found between groups, with no evidence of heterogeneity. • No related fatal SAE was reported in any studies included.		
		Two-dose quadrivalent MMRV Priorix-Tetra (GSK) at interval of 4 weeks to 6mths	Total: 7 studies RCT (n=7)	One-dose MMRV	NR	Safety - solicited local symptoms: pain, redness, swelling	**Safety (pain, redness, swelling)** • 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)** • 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Ma[185] 2015b 10.1016/j.vaccine.2015.06.009 Not funded From earliest date available to 12 December 2014.	Searched for studies in all children aged 0-6yrs – retrieved studies in healthy children aged 9-24mths.	**First dose quadrivalent MMRV** (Brand not specified)	Total: 4 studies RCT (n=4)	MMR	0-42 days	Safety - febrile seizures	**Febrile seizures** • Pooled incidence: ○ MMRV: 1.95% (5/2566) ○ MMR: 1.81% (2/1104) • Pooled Risk Difference: -0.40 (95% CI: -4.20 to 3.40) • Pooled Risk Ratio: 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. 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 studies. More post-marketing	**Risk of bias** 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 max. of 5). The quality of observational studies was assessed using the Newcastle-Ottawa Scale
			Total: 2 studies RCT (n=2)		7-10 days		**Febrile seizures** • Pooled incidence: ○ MMRV: 0% (0/542) ○ MMR: 0% (0/275) • Pooled Risk Difference: 0 (95% CI: -7.98 to 7.98) • Pooled Risk Ratio: 0.51 (95% CI: 0.03 to 8.08)		
			Total: 5 studies RCT (n=5)		0-42 days	Safety - vaccine-related febrile seizures	**Vaccine-related febrile seizures** • Pooled incidence: ○ MMRV: 0.59% (3/5055) ○ MMR: 0.22% (1/4598) • Pooled Risk Difference: 0.58 (95% CI: -0.78 to 1.94) • Pooled Risk Ratio: 1.39 (95% CI: 0.39 to 4.98)		
			Total: 5 studies RCT (n=5)		7-10 days		**Vaccine-related febrile seizures** • Pooled incidence: ○ MMRV: 0.59% (3/5055) ○ MMR: 0.22% (1/4598) • Pooled Risk Difference: 0.58 (95% CI: -0.78 to 1.94)		

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 Ratio: 1.39 (95% CI: 0.39 to 4.98)	studies based on rigorously prospective study design are needed to confirm the findings.	(NOS). All cohort studies included had at least 8 stars (out of a max. of 9) using NOS. **Overall quality of evidence assessment** Not conducted
		First dose quadrivalent MMRV plus other vaccines (Brand not specified)	Total: 5 studies RCT (n=5)	Other vaccines	0–28/42 days	Safety - febrile seizures	**Febrile seizures** • Pooled incidence: ○ MMRV + others: 1.59% (3/1886) ○ Others: 0% (0/2745) • Pooled Risk Difference: 1.70 (95% CI: -1.43 to 4.82) • Pooled Risk Ratio 2.52 (95% CI: 0.63 to 10.11)		
			Total: 5 studies RCT (n=5)		7-10 days		**Febrile seizures** • Pooled incidence: ○ MMRV + others: 0.53% (1/1886) ○ Others: 0% (0/2745) • Pooled Risk Difference: 0.35 (95% CI: -2.12 to 2.81) • Pooled Risk Ratio: 1.41 (95% CI: 0.28 to 7.19)		
			Total: 6 studies RCT (n=6)		0–28/42 days	Safety - vaccine-related febrile seizures	**Vaccine-related febrile seizures** • Pooled incidence: ○ MMRV + others: 0.38% (1/2651) ○ Others: 0% (0/3534) • Pooled Risk Difference: 0.37 (95% CI: -1.61 to 2.35) • Pooled Risk Ratio: 1.46 (95% CI: 0.34 to 6.25)		
			Total: 6 studies RCT (n=6)		7-10 days		**Vaccine-related febrile seizures** • Pooled incidence: ○ MMRV + others: 0.38% (1/2651) ○ Others: 0% (0/3534) • Pooled Risk Difference: 0.37 (95% CI: -1.61 to 2.35)		

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 Ratio: 1.46 (95% CI: 0.34 to 6.25)		
		Second dose quadrivalent MMRV (Brand not specified)	Total: 2 studies RCT (n=2)	MMR	0-42 days	Safety - febrile seizures	**Febrile seizures** • Pooled incidence: ○ MMRV: 1.43% (1/700) ○ MMR: 3.28% (1/305) • Pooled Risk Difference: -1.89 (95% CI: -11.50 to 7.72) • Pooled Risk Ratio: 0.41 (95% CI: 0.05 to 3.27)		
			Total: 2 studies RCT (n=2)		7-10 days		**Febrile seizures** • Pooled incidence: ○ MMRV: 1.43% (1/700) ○ MMR: 0% (0/305) • Pooled Risk Difference: 1.20 (95% CI: -6.30 to 8.69) • Pooled Risk Ratio: 0.80 (95% CI: 0.07 to 9.20)		
			Total: 5 studies RCT (n=5)		0-42 days	Safety - vaccine-related febrile seizures	**Vaccine-related febrile seizures** • Pooled incidence: ○ MMRV: 0.20% (1/5119) ○ MMR: 0% (0/1575) • Pooled Risk Difference: 0.21 (95% CI: -1.91 to 2.33) • Pooled Risk Ratio: 0.47 (95% CI: 0.09 to 2.32)		
			Total: 5 studies RCT (n=5)		7-10 days		**Vaccine-related febrile seizures** • Pooled incidence: ○ MMRV: 0.20% (1/5119) ○ MMR: 0% (0/1575) • Pooled Risk Difference: 0.21 (95% CI: -1.91 to 2.33) • Pooled Risk Ratio: 0.47 (95% CI: 0.09 to 2.32)		
		Second dose quadrivalent MMRV	Total: 1 study RCT (n=1)	Other vaccines	0-28 days	Safety - febrile seizures	**Febrile seizures** • Incidence:		

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
		plus other vaccines (Brand not specified)					○ MMRV + others: 0% (0/347) ○ Others: 0% (0/1453) • Risk Difference: 0 (95% CI: -4.09 to 4.09) • Risk Ratio: 4.18 (95% CI: 0.08 to 210.43)		
			Total: 1 study RCT (n=1)		7-10 days		**Febrile seizures** • Incidence: ○ MMRV + others: 0% (0/347) ○ Others: 0% (0/1453) • Risk Difference: 0 (95% CI: -4.09 to 4.09) • Risk Ratio: 4.18 (95% CI: 0.08 to 210.43)		
			Total: 1 study RCT (n=1)		0-28 days	Safety - vaccine-related febrile seizures	**Vaccine-related febrile seizures** • Incidence: ○ MMRV + others: 0% (0/347) ○ Others: 0% (0/1453) • Risk Difference: 0 (95% CI: -4.09 to 4.09) • Risk Ratio: 4.18 (95% CI: 0.08 to 210.42)		
			Total: 1 study RCT (n=1)		7-10 days		**Vaccine-related febrile seizures** • Incidence: ○ MMRV + others: 0% (0/347) ○ Others: 0% (0/1453) • Risk Difference: 0 (95% CI: -4.09 to 4.09) • Risk Ratio: 4.18 (95% CI: 0.08 to 210.42)		
		At least one dose quadrivalent MMRV (in children aged 10-24mths) ProQuad (n=1 study) Priorix-Tetra (n=2)	Total: 2 studies Retrospective cohort (n=2)	MMR	7-10 days	Safety - seizure	**Seizure** • Relative Risk (RR) (95% CI) ○ Study 1: RR 3.21 (2.20 to 4.67) ○ Study 2: RR 1.90 (1.43 to 2.53)*		

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
		NR = 1	Total: 2 studies Retrospective cohort (n=2)		0-42 days		**Seizure** • Relative Risk (RR) (95% CI) ○ Study 1: RR 2.91 (1.77 to 2.71) ○ Study 2: RR 1.40 (1.19 to 1.65)*		
			Total: 1 study Retrospective cohort (n=1)		7-10 days	Safety - febrile seizure	**Febrile seizure** • Adjusted Relative Risk (95% CI): 2.36 (1.03 to 5.38)		
			Total: 2 studies Retrospective cohort (n=1); Matched cohort (n=1)		5-12 days		**Febrile seizure** • Pooled Relative Risk (95% CI): 2.32 (1.49 to 3.60)		
			Total: 2 studies Retrospective cohort (n=1); Matched cohort (n=1)		0-42 days		**Febrile seizure** • Pooled Relative Risk (95% CI): 1.27 (0.98 to 1.66)		
		At least one dose quadrivalent MMRV (in children aged 4-6yrs) ProQuad (n=1)	Total: 1 study Retrospective cohort (n=1)	MMR	7-10 days	Safety - seizure	**Seizure** • Relative Risk (95% CI): 2.46 (0.76 to 7.97)		
			Total: 1 study Retrospective cohort (n=1)		0-42 days		**Seizure** • 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Marin[186] 2019 10.1542/peds.2019-1305. 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. The authors have indicated they have no financial relationships relevant to this	Immunocompetent children who received varicella vaccine 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** Case #1: • 1yr old developed 2 vesicular lesions 14 days post-vaccination (index case). • 4mth old sibling developed a rash with 25 lesions 19 days after index case rash onset (vOka laboratory confirmed). Case #2: • 1yr old developed 12 vesicular lesions 17 days post-vaccination. • 35yr old father developed >100 lesions 17 days after index case rash onset (vOka laboratory confirmed). Case #3: • 1yr old developed ~30 vesicular lesions 24 days post-vaccination. • 30yr old pregnant mother (gestation 5-6wks) developed 100 vesicular lesions with no fever 16 days after index case rash onset (vOka laboratory confirmed).	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** Not conducted **Overall quality of evidence assessment** 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
article to disclose From database inception to 31 December 2018							• Mother terminated the pregnancy. Fetal tissue was negative for VZV by PCR.		
			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** Case #1: • 20mth old developed HZ 5mths after varicella vaccination. • 35yr old father developed a generalized varicella-like rash, positive for vOka, with an uncountable number of lesions 14 days after HZ onset; father reported varicella in childhood. Case #2: • 3yr old developed HZ 2yrs after varicella vaccine. • 2yr old unvaccinated brother had a rash with 10-20 papulovesicles and fever 19 days after HZ onset. • DNA sequence of skin lesion specimens from the brother matched those of vOka in vaccine received by his older sibling. Case #3: • 5yr old developed HZ 13mths after varicella vaccination. • 23yr old teacher developed varicella with 50–100 vesicular lesions and a 1-day, low-grade fever 17 days later after HZ onset. • Molecular typing of DNA from vesicular fluid from the		

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
							teacher's rash showed vOka with the same characteristics as the vaccine received by the child. Case # 4: • 3yr old developed HZ 5mths after varicella vaccination. • Brother (age not reported) who received varicella vaccine at the same time developed ~50 vesicular lesions 14 days after HZ onset in his sibling. • Virus isolated from brother's skin lesions was confirmed as vOka. Case #5: • 2yr old developed HZ 8mths after varicella vaccination (MMRV vaccine). • 28yr old mother developed a maculopapular and vesicular rash in a non-dermatomal distribution 2 weeks after HZ onset. • 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	**Unconfirmed vOka transmission** Case #1: • 15mth old developed vesicular rash 1 week post-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
						document vOka)	• 51yr old household contact of index case with history of renal transplant; developed "mild varicella" 40 days after vaccination of index case. • Evidence for possible vOka transmission includes seroconversion, positive result of tzanck smear of lesion, clinical varicella. Case #2: • 2yr old with no post-vaccination rash reported. • 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. • No direct exposure of the father to the virus was identified. • Evidence for possible vOka transmission includes positive VZV PCR result from lesion (not typed), clinical varicella. Case #3: • 9mth old with generalized nonvesicular rash 1 week post-vaccination. • Mother developed mild varicella (<30 lesions) 11 days after daughter's vaccination; no laboratory testing was done.		

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 for possible vOka transmission includes clinical varicella. Case #4: • 2 children (ages not reported) vaccinated with no post-vaccination rash reported. • 32yr old pregnant mother (gestation 39 weeks) developed generalised maculopapular vesicular pustular rash 6 days after her children were vaccinated. • 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
New Zealand National Health Committee[174] 2012 DOI: NR; Link: https://www.moh.govt.nz/notebook/nbbooks.nsf/0/1BA074BCCABF911ACC257F7F000A4101/$file/nhc-varicella-vaccine-assessment-report.pdf Funding: Review conducted by an independent statutory authority 1 January 2009 to 16 September 2011 (HTA Agency & repositories); to 2 November	Children aged 0-5yrs	**One-dose** (vaccine type NR)	Total: 1 study Study type NR	NR	NR	Safety (herpes zoster)	**Safety - herpes zoster** • 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** Not conducted **Overall quality of evidence assessment** Not conducted
		Two-dose quadrivalent MMRV	Total: 1 study RCT (n=1)	Interval between doses	NR	Safety of varicella vaccine (tolerance)	**Safety - tolerance** • 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 12mths.		
		At least one-dose monovalent and quadrivalent MMRV Varivax (1 study) (Dosage NR)	Total: 2 studies 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** • 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.		

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
2011 (MEDLINE & Cochrane and 16 November 2011 (EMBASE)							• 5yr 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 (Dosage NR)	Total: 1 study RCT: n=1	NR	NR	Safety of varicella vaccine (tolerance)	**Safety - tolerance** • MMRV vaccine is well tolerated when administered either subcutaneously or intramuscularly to children in the 2nd year of life.		
			Total: 2 studies 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** • Co-administration of MMRV with tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine during the 2nd year of life has shown to be well tolerated. • 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Pallas[163] 2011 Not published 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	Human subjects vaccinated with VZV vaccine	**One-dose monovalent MMR+V** (various brands)	Total: 1 study RCT (n=1)	MMR	NR	Safety (any adverse event)	**Safety (any adverse event)** • Proportion of children experiencing at least one adverse event did not differ considerably between recipients MMR+V (75.6%) and MMR (78.0%). • 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** 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. **Overall quality of evidence assessment** No overall quality of evidence assessment
			Total: 2 studies RCTs (n=2)			Safety (short-term effects of vaccination – local adverse events)	**Safety (local adverse events)** • Both studies reported a higher incidence of injection-site adverse events at varicella vaccine injection sites than at MMR-injection sites. • 1 study reported higher incidence of injection-site adverse events when MMR+V is given concomitantly than 6 weeks apart.		
			Total: 3 studies RCT (n=2) Feasibility (n=1)			Safety (short-term effects of vaccination – local adverse events: pain, redness and swelling)	**Safety (pain, redness, swelling)** • 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). • No differences were observed between		

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
additional study is added here. PubMed: 1 September 1995 to 1 September 2010 Embase: 1995 to 2011 Cochrane Library: 2000 to 2010							monovalent varicella vaccine types (n=1 study).		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).
			Total: 4 studies RCT (n=4)			Safety (systemic adverse events)	**Safety (systemic adverse events)** • 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. • Comparable proportions of specific systemic adverse experiences during days 1 to 43 after vaccination in MMR+V (59.1%) and MMR (60.0%) recipients.		
			Total: 5 studies RCT (n=5)			Safety (systemic adverse events – fever and rash)	**Safety (fever and rash)** • Fever and rash were not different between recipients of MMR+V and MMR. Rashes were reported very infrequently (n=3 studies). • 1 study reported a slightly higher incidence of fever in recipients of varicella vaccine and MMR (MMR+V) than in recipients of MMR. • 1 study reported that fever (≥38.8°C) occurred in 9.4% of all MMR+V recipients and 9.9% of all MMR recipients. • 1 study reported on the incidence of fever in Australian children receiving MMR+V (66.2%) and 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
							(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 RCT (n=1)	NA	NR	Safety (systemic adverse events)	**<u>Safety (systemic adverse events)</u>** • 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.		
		One-dose quadrivalent MMRV	Total: 1 study RCT (n=1)	MMR	NR	Safety (any adverse event)	**Safety (any adverse event)** • Proportion of children experiencing at least one adverse event did not differ considerably between recipients of MMRV (77.6%) and MMR (78.0%). • No vaccine-related serious adverse experiences were reported.		
			Total: 2 studies RCT (n=2)			Safety (local adverse events)	**Safety (local adverse events)** • Two studies reported no difference in the frequency of local adverse events between recipients of MMRV and MMR. • One study found that swelling occurred more in MMRV recipients than 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
							recipients although evidence is not conclusive.		
			Total: 4 studies RCT (n=4)			Safety (systemic adverse events)	**Safety (systemic adverse events)** • 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. • 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 RCT (n=2)			Safety (systemic adverse events: fever and rash)	**Safety (fever and rash)** • 1 study reported that fever (≥38.8 °C) occurred in 10.2% of all MMRV recipients and 9.9% of all MMR recipients. • 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 recipients and in 29.9% of all MMR recipients.		
		Two-dose quadrivalent MMRV	Total: 2 studies RCT (n=1); Review (n=1)	MMR	NR	Safety (local adverse events: pain)	**Safety (pain)** • After a 2nd dose of either MMRV or MMR, a significantly higher proportion of subjects		

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
							experience pain in the MMRV group.		
			Total: 3 studies RCT (n=2); Review (n=1)			Safety (local adverse events: redness and swelling)	**Safety (redness and swelling)** • 2nd dose of MMRV significantly increased the likelihood of developing redness compared with a 2nd dose of MMR. • 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 RCT (n=2);			Safety (systemic adverse events)	**Safety (systemic adverse events)** • 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 RCT (n=3); Review (n=1)			Safety (systemic adverse event: fever)	**Safety (fever)** • Incidence of fever after 2nd dose did not differ between groups.		
		At least one-dose monovalent or quadrivalent MMRV	Total: 5 studies RCT (n=5);	MMR	NR	Safety (systemic adverse events)	**Safety (systemic adverse events)** • Overall, the included studies showed that the proportion of subjects with systemic adverse events was comparable in vaccination groups.		

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 RCT (n=2)			Safety (systemic adverse events: fever)	**Safety (fever)** • The incidence of fever following varicella vaccination (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)** • 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)** • 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)** • 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)** • 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Panozzo[187] 2019 10.1016/j.vaccine.2018.06.067 Partially supported by the World Health Organization (WHO) From database inception to 28 May 2015 for searches except PubMed (to 3 December 2017)	Protocol: Individuals experiencing arthritis and/or arthralgia following immunisation Included study: Privately insured children, 12-23mths of age; (USA, 2000–2012)	**At least one-dose (monovalent and quadrivalent)** Varivax (Merck) monovalent vaccine and MMRV quadrivalent (unspecified): 1 study* *Both vaccines included in the same study	Total: 1 study Retrospective cohort (n=1)	NA	Up to 180 days	Safety - arthritis or arthralgia (composite outcome)	**Safety - cases of arthritis or arthralgia** • Doses administered: ○ MMRV: 123,200 ○ MMR+V: 584,987 • Number of cases: ○ 1 case of arthritis/arthralgia after MMRV and 1 case after MMR+V 1-42 days post-vaccination in primary analyses ○ 1 case of arthritis/arthralgia after MMRV and 3 cases after MMR+V 1-42 days post-vaccination in secondary analyses ○ 6 cases of arthritis/arthralgia after MMRV and 25 cases after MMR+V 57-180 days post-vaccination in secondary analyses. • Primary analyses used stratified exact binomial tests and secondary analyses used case-centred 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** Not conducted **Overall quality of evidence assessment** 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Phuong[188] 2017 10.1016/j.vaccine.2016.09.033 Italian Medicines Agency (AIFA) From database inception to June 2016	Kawasaki disease cases following vaccination	**At least one dose quadrivalent** Brand not specified	Total: 1 study Retrospective cohort (n=1)	NA	NR	Safety - Kawasaki Disease	**Safety – Kawasaki Disease (KD)** • 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. • 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** Not conducted **Overall quality of evidence assessment** 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Skull[162] 2001 10.1136/adc.85.2.83 Funding: NR 1966 to December 2000	Human subjects vaccinated with VZV vaccine	**One-dose** (vaccine type NR)	Total: 21 studies RCTs (n=6) Prospective cohort (n=14) Post-licensure study (n=1)	Placebo and no vaccination	Up to 7yrs (1 RCT) 1 to 19.6yrs (cohort studies)	Safety (deaths)	**Safety - deaths** • 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. • 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** Studies were systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care. The results for individual studies are not provided. The quality of evidence in studies included in this analysis was reported as generally good. However, the following methodological issues were identified. Loss of subjects from analysis was sometimes
		One-dose (vaccine type NR)	Total: 21 studies RCTs (n=6) Prospective cohort (n=14)	Placebo and no vaccination	Up to 7yrs (1 RCT) 1 to 19.6yrs (cohort studies)	Safety (deaths)	**Safety - deaths** • Although controlled trials confirm approximately 100% relative risk reduction for severe disease, no		

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 study (n=1)				deaths have been reported for subjects in either vaccine or placebo groups. • 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.		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. 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
		2nd dose (vaccine type NR)	Total: 3 studies Study type: NR	1st dose (vaccine type NR)	NR	Safety (reactions)	**Safety - reactions** • A second dose of vaccine appears to cause fewer reactions than the first.		
		NR	Total: 3 studies RCT (n=3)	Placebo	NR	Safety (short-term effects)	**Safety - short-term effects** • 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.		

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
							• 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.		or duration of follow up, suggesting a true effect. **Overall quality of evidence assessment** 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
		NR	Total: NR Study type (RCT, nRCT, post licensure study)	Placebo	NR	Safety (serious adverse events)	**Safety - serious adverse events** • No serious adverse events have been reported in controlled trials. • 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 Oka/Merck vaccine reported for some studies	Total: 13 studies RCT (n=1); Prospective cohort (n=1); Other cohort (n=8); Case series: (n=1); Post-licensure adverse event reporting system (n=1); Unknown: (n=1);	Placebo	Up to 9mths for RCT Up to 19yrs 7mths for cohort studies	Safety (herpes zoster)	**Safety - herpes zoster** • In 1 RCT, no cases of herpes zoster were noted in either placebo or vaccine recipients after 9mths (732 person years). • A single prospective cohort study of children has reported a mild case of zoster in 1 of 854 children after vaccination (duration of follow up unknown).		

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
							• 7 other cohort studies report no zoster for as much as 19yrs 7mths, or 3277 person years after vaccination. • Two mild cases of zoster (no virus isolated) were reported in healthy children (aged 2 and 4yrs) following vaccination with Oka/Merck vaccine and a rate of 21 cases/100,000 person-years was estimated for Oka/Merck recipients to that time, compared with an expected rate of 77/100,000 person years in school aged children following natural chickenpox. • 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. • 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). • The US post-licensure Vaccine Adverse Event Reporting System		Level II-I Evidence from 12 well designed cohort studies.

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
							suggests a rate of 2.6/100,000 vaccine doses distributed.		
		NR	Total: 5 Studies Study type: RCT (n=1), nRCT (n=1), Case report (n=1), Post licensure study (n=1) Other (n=1)	Placebo	NR	Safety (varicella transmission from vaccinated individuals)	**Safety - varicella transmission from vaccinated individuals** • No clinical trials have shown transmission of vaccine related VZV between immunocompetent individuals. • One placebo controlled RCT found seroconversion, but no disease in 3/439 placebo vaccinated siblings of 465 VZV vaccine recipients. Natural infection or subclinical spread of vaccine virus may have occurred. • In a small controlled trial, no evidence of transmission or boosting in unvaccinated seronegative and seropositive close contact were found. • Case report of transmission has been reported rarely from children with varicella like rash following vaccination. • Reported transmission of vaccine strain virus from		

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
							a vaccinated child with zoster to their vaccinated sibling, resulting in mild chickenpox. • 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Van den Boogaard[190] 2021 10.1016/j.vaccine.2020.12.079 World Health Organization 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 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** 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. Case report #2: Case of high fever 1 day after MMRV vaccination and seizures 6 days later in a 13mth old girl. 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. 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** Not conducted **Overall quality of evidence assessment** 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. 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 Year DOI Funding source Search dates	Population size Demographics at baseline Setting(s) Location(s)	Vaccine type Vaccine dosage Vaccine brand	Number of studies Study type	Comparator(s)	Follow-up period after vaccination	Safety outcomes	Summary of main findings	From abstract or elsewhere	Yes/No and details if applicable
Yin[160] 2018 doi.org/10.1080/14760584.2018.1433999 Natural Science Foundation of Guangdong Province, China 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 **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)** RR 0.73 (0.57 to 0.93) **RR for incidence of varicella-like rash (95% CI)** 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** 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. **Overall quality of evidence assessment** Not conducted
		2nd dose monovalent	Total: 1 study **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)** RR 0.73 (0.57 to 0.93) **RR for incidence of varicella-like rash (95% CI)** RR 0.40 (0.21 to 0.78)		
		2nd dose quadrivalent MMRV	Total: 5 studies **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)** RR 0.59 (0.54 to 0.64)		
			Total: 6 studies **Self-control** (n=6)		0-42 days after vaccination		**Pooled RR for incidence of fever (any intensity) (95% CI)** RR 0.73 (0.69 to 0.71) Note: Data extracted as reported in systematic review, but 95% CIs do not appear correct.		
			Total: 5 studies **Self-control** (n=5)		0-14 days after vaccination		**Pooled RR for incidence of fever (Grade 3 or ≥ 39.5) (95% CI)** RR 0.32 (0.24 to 0.44)		
			Total: 4 studies **Self-control** (n=4)		0-42 days after vaccination		**Pooled RR for incidence of fever (Grade 3 or ≥ 39.5) (95% CI)** RR 0.61 (0.46 to 0.83)		
			Total: 4 studies **Self-control** (n=4)		0-42 days after vaccination		**Pooled RR for incidence of varicella-like rash (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
							RR 0.32 (0.16 to 0.62)		
		2nd dose quadrivalent MMRV	Total: 6 studies **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)** RR 0.89 (0.73 to 1.08)		
			Total: 3 studies **Self-control** (n=3)				**Pooled RR for incidence of pain (Grade 3) (95% CI)** RR 2.05 (0.19 to 22.60)		
			Total: 6 studies **Self-control** (n=6)				**Pooled RR for incidence of redness (any) (95% CI)** RR 1.00 (0.88 to 1.14)		
			Total: 3 studies **Self-control** (n=3)				**Pooled RR for incidence of redness (Grade 3) (95% CI)** RR 4.93 (1.89 to 12.87)		
			Total: 6 studies **Self-control** (n=6)				**Pooled RR for incidence of swelling (any) (95% CI)** RR 1.34 (1.06 to 1.66)		
			Total: 3 studies **Self-control** (n=3)				**Pooled RR for swelling (Grade 3) (95% CI)** 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 A 3.4 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	n=590 children
MMRV + MenACWY	1 RCT	n=100 children
MMRV + MenC	1 RCT	n=716 children

Source: Bauwens J et al. 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.

Appendix A 3.5 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_2021	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	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 Yes	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 Yes	No	RCTs: Yes	NRSI: No	No	No	Yes	Yes	Yes	Critically Low

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?	
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_2021	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 Yes	No	RCTs: Yes	NRSI: Yes	Yes	Yes	Yes	Yes	Yes	Critically Low

Key: MA – meta-analysis; NA – not applicable; NRSI – non-randomised study of intervention; RCT – randomised controlled trial.

Supplementary Appendix for Chapter 4

Appendix A 4.1 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

Database(s): **EBSCO** 1974 to 2022 June 27

#	Query	Limiters/Expanders	Results
S11	S3 AND S8 AND S9	Limiters - Date of Publication: 20130101-20221231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	234
S10	S3 AND S8 AND S9	Expanders - Apply equivalent subjects 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 Search modes - Boolean/Phrase	1,340,535
S8	S4 OR S5 OR S6 OR S7	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	790,993
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 Search modes - Boolean/Phrase	305

S6	(MH "Chickenpox Vaccine+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,156
S5	(MH "Vaccination+") OR (MH "Immunization+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	197,721
S4	AB (vaccin* OR immuni* OR inocula*) OR TI (vaccin* OR immuni* OR inocula*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	734,433
S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	18,353
S2	(MH "Chickenpox")	Expanders - Apply equivalent subjects 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 Search modes - Boolean/Phrase	17,180

Appendix A 4.2 Data extraction tables

General study characteristics	**Author Name, Year of Publication, DOI**	Akpo et al. 2020[213] 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 Note: Contact pattern data were obtained from the POLYMOD study.[216]	
	Perspective	1. Societal 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 quad + quad: 1st dose quad at 12mths; 2nd dose quad at 3yrs 4mths	
	Coverage rate	mono + quad: 87% for 1st dose and 2nd dose 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% Efficacy (MSD vaccines): 1-dose: 78%; 2-dose 98.3%	
	Waning	1st dose 30yrs; 2nd dose permanent (progressive immunity)	
	Costs included	**Type of cost** **Direct costs** • GP visits (varicella, BV, wildtype and breakthrough HZ) • Hospitalisation (varicella, BV, wildtype and breakthrough HZ) • Vaccine ○ Vaccine administration	**Measurement and valuation** **Direct costs** • % of varicella cases with GP visits, number of visits per case, cost per visit (including treatment cost) for varicella • Relative propensity (compared to wildtype) for breakthrough varicella to consult GP, number of GP visits per

		○ Extra time for monovalent vaccine ○ GP visits (related to vaccine adverse events except febrile seizures) ○ Emergency rooms visits (related to febrile seizures) **Indirect costs** • Productivity loss associated with varicella, BV and HZ	breakthrough varicella case, cost per visit (including treatment cost) for varicella • % of HZ cases with GP visits, number of visits per case, cost per visit for HZ • Relative propensity (compared to wildtype) for breakthrough HZ to consult GP • Cost for medication and GP visit for PHN • % of varicella cases hospitalised, hospital length of stay for varicella, cost of hospitalisation day for varicella • Relative propensity (compared to wildtype) for breakthrough hospitalised varicella • % of HZ cases hospitalised, hospital length of stay for HZ, cost of hospitalisation day for HZ • Relative propensity (compared to wildtype) for breakthrough hospitalised HZ • Price per vaccine dose • Cost of vaccine administration • Cost of extra time for monovalent vaccine • Injection site adverse events (%) and risk of febrile seizure • % 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) **Indirect costs** • Number of days off work secondary to varicella, BV and HZ

			• Mean income
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Incidence of varicella and BV • Incidence of HZ (wildtype and breakthrough) with and without PHN (by age) • Age at varicella and HZ infection **Indirect effects** • Incidence of HZ (exogenous boosting)	**<u>Measurement and valuation</u>** **Indirect effects** • % of effective varicella contacts that boost against HZ by age (0-49yrs, 50-69yrs, 70-79yrs, 80+yrs) • Duration of boosting (2yrs) against HZ based on calibration **QALY loss per case** • Varicella by age (0-14yrs and 15yrs+) • BV • HZ or breakthrough HZ without PHN by age (0-14yrs, 15-44yrs, 45-64yrs, 65+yrs) • 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. 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). 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.

General study characteristics	**Author Name, Year of Publication, DOI**	Azzari et al. 2020[214] 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 Note: Model used a MSEIRS structure (Maternal/Passive Immunity-Susceptible-Exposed-Infectious-Recovered-Susceptible). Model segmented into seven age groups (<1yrs, 1-4yrs, 5-9yrs, 10-14yrs, 15-44yrs, 45-64yrs, ≥65yrs). Contact pattern data were derived assuming proportionate mixing, that is, mixing between age groups is proportional to their activity level. 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 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) 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% 2nd dose quad: 83%
Model input parameters	**Efficacy/effectiveness**	Efficacy MSD ProQuad® vaccine: 1-dose 100%; 2-dose 100% Efficacy GSK Priorix-Tetra® vaccine: 1-dose 65.4%; 2-dose 94.9% Strategy A: 1-dose 100%; 2-dose 100% Strategy B: 1-dose 100%; 2-dose 100% Strategy C: 1-dose 75%; 2-dose 95% 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)

		GSK Priorix-Tetra® vaccine: 1st dose 5.88% p.a. (1/17yrs); 2-dose lifetime immunity Strategy A: 1-dose 4% p.a.; 2-dose 1.3% p.a. Strategy B: 1-dose 4% p.a.; 2-dose 1.3% p.a. Strategy C: 1-dose 6.7% p.a.; 2-dose 2% p.a. Strategy D: 1-dose 6.7% p.a.; 2-dose 2% p.a.	
	Costs included	**Type of cost** **Direct costs** • Outpatient visits (varicella) • Hospitalisation (varicella) • Prescription and OTC drugs per inpatient and outpatient • Diagnostic tests per inpatient and outpatient • Vaccines • Delivery, cold-chain and administration of monovalent vaccine • Febrile seizures associated with quadrivalent vaccine **Indirect costs** • Productivity loss associated with varicella for outpatients and inpatients (ages 15 to 64yrs only) • Productivity loss for caregivers of outpatients (cases aged <15yrs) • Productivity loss for caregivers of inpatients (cases aged <15yrs)	**Measurement and valuation** **Direct costs** • % of cases requiring an outpatient visit and cost per visit • % of varicella cases hospitalised, number of days per hospitalisation and cost per day • Total cost of prescription/OTC drugs per inpatient and outpatient • Total cost of diagnostic tests per inpatient and outpatient • Cost of vaccines estimated as 50% of the net maximum selling price • Total cost of administration, delivery and cold storage • 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 **Indirect costs** • Days of work lost and average cost per workday missed
	Effects included	**Type of Effects** **Direct effects** • Incidence of varicella • Hospitalised cases • Death • Incidence of HZ	**Measurement and valuation** **Direct effects** • NR **QALY loss per case** • Varicella and BV

		Indirect Effects • NR	• HZ and breakthrough HZ • 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. 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.

General study characteristics	**Author Name, Year of Publication, DOI**	Heininger et al. 2021[212] 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 Note: Model adapted from other studies including that used in Azarri et al. 2020 (Italy)[214] and used a static population size and age distribution. Contact pattern data were projected from POLYMOD data.[216] 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 2. Health care payer	
	Time horizon	Base case 50yrs (also considered 25yrs and 100yrs)	
	Comparator(s)	1. No vaccination 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); Strategy 2: 1st dose at 12mths (MMRV), 2nd dose at 19mths (MMRV); 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** **Direct costs** • Inpatient and outpatient visits • Treatments • Diagnostics • Hospitalisation • Vaccine • Administration, delivery and cold-chain requirements for varicella only vaccine	**Measurement and valuation** **Direct costs** • % of cases requiring outpatient visits, number of outpatient visits per case (all by age) and cost per outpatient visit • % of cases requiring hospitalisation, mean duration of hospital stay and mean cost per hospital day (all by age) • % of outpatient cases requiring prescription or OTC medication and

		(assumed MMRV vaccine given instead of current MMR vaccine and therefore no additional cost) • Febrile seizure (MMRV vaccine) • Treatment for HZ (uncomplicated and complicated with PHN) **Indirect costs** • Productivity loss for those ill with varicella • Productivity loss for carers of those with varicella • Productivity loss for those ill with HZ	mean cost of each for outpatients (all by age) • % of cases requiring diagnostic test and mean cost of diagnostic test per case • Incidence of HZ, % of HZ cases that develop PHN and mean cost per case of HZ (uncomplicated and complicated with PHN) (all by age) **Indirect costs** • Mean days lost from work (outpatient and inpatient) (by age) and mean cost per work day missed for productivity losses • Febrile seizure – number of cases per dose and cost per case
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Cases of varicella • Hospitalisations • Deaths • HZ **Indirect effects** • NR	**<u>Measurement and valuation</u>** **QALY loss per case** • Reported per case for each vaccination strategy but not for each health effect
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; CHF – swiss franc; CUA – cost-utility analysis; HZ – herpes zoster; MMRV – measles, mumps, rubella, varicella; NR – not reported; PHN – post herpetic neuralgia; QALY – quality-adjusted life year; UVV – universal varicella vaccination.

General study characteristics	**Author Name, Year of Publication, DOI**	Littlewood et al. 2015[208] 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. Note: No empirical French data were available for the contact matrix, so Italian POLYMOD data were used.[216] 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 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** **Direct costs** • GP/outpatient/home visits (varicella and HZ) • Medication (varicella and HZ) • Additional examinations (varicella) • Laboratory tests (HZ) • Hospitalisation (varicella and HZ) • Vaccine (varicella)	**Measurement and valuation** **Direct costs** • % 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 • Weighted average of hospital costs per case (including all complications) for varicella and HZ

		• Adverse events associated with vaccine (febrile seizures) **Indirect costs** • Workdays lost for parents of children with varicella • Alternative childcare arrangements • Workdays lost for adults patients with varicella and HZ	• Cost per dose of vaccine • % with febrile seizure after vaccine and hospitalised cost per case **Indirect costs** • Varicella - % whose parents lost work time, workdays lost per case, % with alternative childcare costs (age <18yrs) • Varicella - % who lost work time, workdays lost per case, % of breakthrough cases with indirect costs (age 18-65yrs) • HZ - % who lost work time, workdays lost per case, % of breakthrough cases with indirect costs • Cost of alternative childcare • Cost per workday lost
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Cases of varicella and BV (age-specific) • Cases of HZ and breakthrough HZ • Hospitalised cases (varicella and BV) • Complications (varicella and BV) • Death (varicella and BV) **Indirect effects** • Impact on incidence of HZ (exogenous boosting)	**<u>Measurement and valuation</u>** **Direct effects** • % of cases hospitalised (varicella, BV, HZ and breakthrough HZ) • Mean number of complications per varicella and zoster case (by age) and relative propensity for breakthrough to cause complications • Mean number of deaths per varicella (all ages) and zoster (by age) case and relative propensity for breakthrough to cause death **Indirect effects** • Age-specific rates of exogenous boosting (<50yrs, 50-64yrs, >65yrs) **QALY loss per case** • Varicella (by age: 0-14yrs; ≥15yrs)

			• BV (all ages) • HZ with and without PHN by age (0-59yrs, 60-64yrs, ≥65yrs) • 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.

General study characteristics	**Author Name, Year of Publication, DOI**	Melegaro et al. 2018[215] 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) 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. The contact matrices were based on a synthetic matrix derived from age specific contact patterns and validated through comparison with POLYMOD results.[216] 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** **Direct costs** ▪ GP visits (varicella and HZ) ▪ Treatment ▪ Hospitalisation ▪ Vaccine cost ▪ Vaccine administration cost **Indirect costs** ▪ NA	**Measurement and valuation** **Direct costs** ▪ Number of GP consultations per varicella case (by age - <14yrs and ≥14yrs) and BV case (all ages), consultation cost and treatment cost per case ▪ Hospitalisation rate for varicella, propensity for BV to cause hospitalisation, hospitalisation cost per case of varicella (by age - <14yrs and ≥14yrs)

			▪ Outpatient cost per case of HZ (incl. visit, treatment and diagnostics) ▪ Outpatient cost per case of PHN (incl. visit, treatment and diagnostics) ▪ Hospitalisation cost per case of HZ (by age - <49yrs and ≥50yrs) ▪ Hospitalisation cost per case of PHN (by age - <49yrs and ≥50yrs) ▪ Cost per dose of vaccine ▪ Admin cost per dose of vaccine **Indirect costs** ▪ NA
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Averted cases of varicella (incl. BV) and HZ (with and without PHN) • Averted deaths **Indirect effects** • Impact on incidence of HZ (exogenous boosting – progressive partial immunity [PI] and temporary full immunity [TI])	**<u>Measurement and valuation</u>** **<u>Indirect effects</u>** • 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 • Temporary full immunity - each boosting event provides partial complete immunity to HZ. **Utilities (varicella only) and QALY loss per case** • Varicella (by age: 0-14yrs; ≥15yrs) • Reduction in QALY loss for mild versus severe varicella • HZ by age (20yrs, 40yrs, 60yrs, 80yrs) • PHN by age • 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. 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 (ICER €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.

General study characteristics	**Author Name, Year of Publication, DOI**	Pawaskar et al. 2021[(210)] 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 Note: Model adapted from elsewhere. Source for contact pattern data not reported. 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. The model was calibrated to the demographic, behavioural, and epidemiological characteristics of the population of Norway.	
	Perspective	1. Healthcare system 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% 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** **Direct costs** • Primary healthcare visits • Hospitalisation • Vaccine • Administration of vaccine **Indirect costs** • Workdays lost due to varicella infection	**Measurement and valuation** **Direct costs** • Unit costs and rates of primary healthcare visits, hospitalisations as reported elsewhere • List price of vaccine • Nurse's time for administration (10 minutes per dose) **Indirect costs** • Mean wage for workdays lost

	Effects included	**<u>Type of Effects</u>** **Direct effects** • Incidence of varicella, BV and HZ • Outpatient cases, hospitalisations and deaths **Indirect effects** • Incidence of HZ (exogenous boosting)	**<u>Measurement and valuation</u>** **Indirect effects** • Duration of boosting: 80yrs • 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 **Utilities and QALY loss per case** • Varicella (by age: <15yrs; ≥15yrs) • BV (by age: <15yrs; ≥15yrs) • Mortality due to varicella (by age: <15yrs, 15-65yrs, ≥65yrs) • Uncomplicated HZ (all ages) • 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.

General study characteristics	**Author Name, Year of Publication, DOI**	Rafferty et al. 2021[152] 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 Note: Contact patterns derived from POLYMOD data.[216]	
	Perspective	1. Societal 2. Health care payer	
	Time horizon	75yrs 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. 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) 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). Probability of 1st dose vaccination: Rejectors (3%), Hesitants (75%), Acceptors (97%). 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** **Direct medical costs** • Physician visit (chickenpox and shingles) • Hospital visit (chickenpox and shingles) • Emergency room visit (chickenpox and shingles)	**Measurement and valuation** **Direct medical costs** • % of chickenpox and shingles cases that will visit a physician and cost per case • % of chickenpox and shingles cases that go to hospital (by age group), average

		• Medication costs (chickenpox and shingles [including PHN]) • Personal expenses (chickenpox) [OTC and prescription medication, travel and gifts] **Vaccination costs** • Vaccine • Febrile seizures (chickenpox) **Indirect costs** • Productivity loss for those ill with varicella and HZ (by age) • Productivity loss for carers of those with varicella (by age)	length of stay and cost per day • % of chickenpox and shingles cases that go to emergency room and cost per visit • % of shingles cases who develop PHN (by age group) and % of cases that last for a certain number of days • Average prescription cost per case of chickenpox and shingles • Personal out of pocket expenses per case of chickenpox (by age group) and shingles **Vaccination costs** • Cost (procurement, labour and supply costs) to vaccinate a child with MMRV vaccine • % of 1st dose chickenpox vaccinations that result in febrile seizure and cost to treat febrile seizure in emergency room **Indirect costs** • Cost per case of chickenpox • Cost per case for hospitalisation with chickenpox • Cost per case of shingles with no PHN • Cost per case of shingles with PHN • Cost per hospitalised case of shingles
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Incidence of varicella and BV • Hospitalised cases of chickenpox • Deaths **Indirect effects** • Main model run twice, once to include and once to exclude impact on incidence of HZ	**<u>Measurement and valuation</u>** **Boosting** • Duration of boosting to HZ: 5yrs (based on empirical data) **Utilities for QALYs** • Baseline utility weight for no pain • Chickenpox (normal) utility weight by age • Chickenpox (breakthrough) utility weight

		(exogenous boosting [EB])	by age • Chickenpox (hospitalised) utility weight by age • Shingles (normal) utility weight • Shingles (PHN) utility weight • 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. SDI and LDI both not cost-effective versus no vaccination (ICUR>$125,000/QALY gained) when the impact on shingles [EB] included. SDI cost-effective versus long-dose schedule (ICUR <$29,000/QALY gained) when the impact on shingles [EB] included. 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]. SDI cost-effective versus LDI (ICUR <$6,000/QALY gained) when the impact on shingles [EB] included. 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.

General study characteristics	**Author Name, Year of Publication, DOI**	van Lier et al. 2015[209] 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 Note: Contact patterns sourced from POLYMOD study.[216]	
	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	**<u>Type of cost</u>** **Direct costs** • GP visits (varicella and HZ) • Hospitalisation (varicella and HZ) • Medication • Varicella vaccine cost • Varicella vaccine introduction cost (e.g. new leaflets, campaign) • Varicella vaccine coordination cost (e.g. variable personnel costs, other materials, printing) **Indirect costs** • Productivity loss due to acute illness by age (<15yrs [their parents] and 15-65yrs)	**<u>Measurement and valuation</u>** **Direct costs** • % 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 • % of HZ cases visiting the GP, unit cost per visit • % of varicella GP visits requiring ED visit (by age - <15yrs and ≥15yrs) unit cost per visit • % of varicella GP visits requiring medical specialist consultation (by age - <15yrs and ≥15yrs), unit cost per visit • % of all varicella cases requiring

		(varicella and HZ) • Productivity loss due to mortality by age (<15yrs and 15-65yrs) (varicella and HZ)	hospitalisation (by age - <15yrs and ≥15yrs), % of all HZ cases requiring hospitalisation, unit cost per day for academic/general hospital, mean duration of stay • % of all varicella and HZ cases requiring hospitalisation with ICU, unit cost per day for academic/general hospital, mean duration of stay • % of all varicella cases requiring OTC medication for antipyretics, unit cost per case • % of all varicella cases requiring OTC medication for skin, unit cost per case • % of all GP visits for varicella requiring antibiotics, unit cost per treatment • number of doses of immunoglobulin for varicella (for 0yr olds and women of reproductive age) required per year at baseline, unit cost per dose **Vaccination costs** • Once-off cost for vaccine introduction • 2 doses of vaccine per vaccine, unit cost per dose • Unit cost of vaccine coordination per vaccination **Indirect costs** • % of all cases with productivity loss for parents of <15yr olds with varicella, number of hours lost, mean unit cost per hour • all cases for productivity loss due to acute illness for 15-65yr olds (varicella and HZ), number of hours lost, unit cost

			per hour depending on age • % of all cases with productivity loss due to mortality (varicella and HZ) by age (15-65yrs and ≥65yrs)
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Incidence of varicella and HZ • Deaths • Vaccine induced VZV reactivation (included in 2/4 scenarios modelled) • Outcomes aggregated to produce QALYs **Indirect effects** • Impact on incidence of HZ (exogenous boosting – included in 2/4 scenarios modelled)	**<u>Measurement and valuation</u>** **QALY loss per case** • Varicella (by age: 0-14yrs; ≥15yrs) • BV (only <15yrs) • Mortality due to varicella (by age: <15yrs, 15-65yrs, ≥65yrs) • HZ acute illness (by age: 20yrs, 40yrs, 60yrs, 80yrs) • 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. 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. 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. Suggests that varicella vaccination is predominantly dominated versus no vaccination when exogenous boosting is assumed and vaccine VZV reactivation is not assumed. 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[(211)] 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 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.[(216)]	
	Perspective	1. Societal 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	**<u>Type of cost</u>** **Direct costs** • Vaccine • Vaccine administration • Primary care consultation for varicella and HZ (including PHN) (by age) • Specialist care for varicella (by age) • Hospitalisation for varicella and HZ (by age) • Antivirals for HZ and medication for PHN • Hospitalisation for stroke as a complication of HZ **Indirect costs**	**<u>Measurement and valuation</u>** **Direct costs** • List price of vaccine • Nurse's time for administration (15 minutes per dose) • Healthcare resource use obtained from study on burden of chickenpox and expert opinion and unit costs obtained from a regional hospital price list • List price of antivirals and medication for HZ **Indirect costs** • Average monthly salary + statutory

		• Productivity loss for those ill with varicella and HZ (by age) • Productivity loss for carers of those with varicella (by age)	employer's fee
	Effects included	**<u>Type of Effects</u>** **Direct effects** • Incidence of varicella, BV and HZ • Outpatient cases • Hospitalisations **Indirect effects** • Incidence of HZ (exogenous boosting) (assumed comparable to live HZ vaccination of limited duration)	**<u>Measurement and valuation</u>** **QALY loss per case** • Varicella (by age) • BV (by age) • 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 A 4.3 Critical appraisal results

Dimension of quality	**Akpo et al.[213]**	**Azzari et al.[214]**	**Heininger et al.[212]**	**Littlewood et al.[208]**
Structure (S)				
S1: Statement of decision problem/objective	Primary decision maker not specified			Primary decision maker not specified
S2: Statement of scope/perspective				
S3: Rationale for structure				
S4: Structural assumptions			Waning immunity not considered. Exogenous boosting not considered.	
S5: Strategies/comparators				
S6: Model type				
S7: Time horizon		50yrs perhaps too short given HZ typically occurs several decades after initial infection and current mortality rates	Base case 50yrs perhaps too short given HZ typically occurs several decades after initial infection and current mortality rates (time horizon subject to SA)	
S8: Disease states/pathways				
S9: Cycle length				
Data (D)				
D1: Data identification		Parameter data used in the model were based on public health reports, peer-reviewed publications, and expert opinion. While some sources are provided, others particularly relating to the underlying epidemiological model are not provided or where they are, sources are not provided	Detailed information on methods of data identification and data sources is generally lacking	
D2: Pre-model data analysis	See model paper			See model paper
D2a: baseline data		Parameter values for movement between epidemiological states are not provided	Baseline data choices are not comprehensively described and justified	

Dimension of quality	**Akpo et al.[213]**	**Azzari et al.[214]**	**Heininger et al.[212]**	**Littlewood et al.[208]**
D2b: treatment effects		Efficacy data has been sourced from single clinical trials only but alternative values have been explored in PSA	Efficacy/effectiveness and waning base case data not reported	
D2c: quality-of-life weights (utilities)		Utility values per health effect not reported	Utility values per health effect not reported	Utility values per health effect not reported
D3: Data incorporation				
D4: Assessment of uncertainty	Overall	Overall	Overall	Overall
D4a: methodological				Different discounting methods
D4b: structural	Vaccine type, time horizon, discount rates, waning immunity	Vaccine type only	Age at vaccination, time horizon and vaccine type	Extended dosing interval, waning rates
D4c: heterogeneity	N/A	N/A	N/A	N/A
D4d: parameter	One-way SA only. No PSA (no justification for not doing so)	PSA (values and distributions provided in suppl. file)	PSA (distributions provided in suppl. file but values not clear)	PSA (values and distributions provided in suppl. file)
Consistency (C)				
C1: Internal consistency		Model validation not described		
C2: External consistency				

Key: HZ – herpes zoster; N/A – not applicable; PSA – probabilistic sensitivity analysis; SA – sensitivity analysis

Dimension of quality	Melegaro et al.[215]	Pawaskar et al.[210]	Rafferty et al.[152]	van Lier et al.[209]	Wolff et al.[211]
Structure (S)					
S1: Statement of decision problem/objective					
S2: Statement of scope/perspective					
S3: Rationale for structure					Simpified model structure provided - no additional supplementary material
S4: Structural assumptions	Waning immunity not considered			Waning immunity not considered	
S5: Strategies/comparators					
S6: Model type					Markov
S7: Time horizon		Base case 50yrs perhaps too short given HZ typically occurs several decades after initial infection and current mortality rates (time horizon subject to SA)			
S8: Disease states/pathways					
S9: Cycle length					
Data (D)					
D1: Data identification					Lacks detail.
D2: Pre-model data analysis					Lacks detail.
D2a: baseline data					Lacks detail.
D2b: treatment effects	Waning data not reported		Efficacy/effectiveness and waning base case data not reported		Source of vaccine effectiveness data not referenced.
D2c: quality-of-life weights (utilities)	Utility values per health effect not reported		Utility values per health effect not reported	Utility values per health effect not reported	Utility values per health effect not reported

Dimension of quality	**Melegaro et al.[215]**	**Pawaskar et al.[210]**	**Rafferty et al.[152]**	**van Lier et al.[209]**	**Wolff et al.[211]**
D3: Data incorporation					
D4: Assessment of uncertainty	Overall	Overall	Overall	Overall	Overall
D4a: methodological				Different discounting methods (i.e. no discounting)	Different discounting methods (i.e. no discounting)
D4b: structural	Different assumptions around EB, fertility rates, time horizon, discount rates	Time horizon, discount rates	Discount rate, waning of immunity	Short-dose interval, discount rates, with and without HZ	Waning of immunity, no boosting, time horizon
D4c: heterogeneity	N/A	N/A	N/A	N/A	N/A
D4d: parameter		PSA but no detail (values and distributions not provided in text or suppl file).	No PSA (no justification for not doing so)	No PSA (no justification for not doing so)	No PSA (no justification for not doing so)
Consistency (C)					
C1: Internal consistency		Model validation not described		Model validation not described	Model validation not described
C2: External consistency					

Supplementary Appendix for Chapter 5

Appendix A 5.1 Detailed Epidemiological Model flows and Parameter Estimation

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, λ(a). The rate of movement from E to the infectious state (I) is given by the duration of the latent period for varicella, σ. The rate of movement from I to the recovered state (R) is given by duration of the infectious period for varicella, γ_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 (SZ) is given by the duration of cell-mediated immunity, δ. Once in Sz, individuals develop herpes zoster and move to the infected zoster state (Iz) at a rate given by an age-dependent reactivation rate, ρ(a). The rate of movement from Iz to the recovered zoster state (Rz) is given by duration of zoster infection, γ_z. Following herpes zoster infection, individuals become permanently immune to herpes zoster and remain in Rz. Under the exogenous boosting theory (examined in a scenario analysis), individuals in Sz state who are exposed to the VZV gain a boost to their cell-mediated immunity and they temporarily move from Sz back to Rv at a rate given by g(a)λ(a)

Varicella vaccination pathway

Three vaccination strategies were tested in the model:

- one-dose - vaccine administered at age 12 months
- two-dose short interval - vaccines administered at age 12 months and 15 months
- two-dose long interval - vaccines administered at age 12 months and five years.

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, λ(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).

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, λ(a).

Parameter estimation through calibration

A number of the epidemiological model input parameters, specifically, the probability of VZV infection given contact and the 16 age-specific herpes zoster reactivation rates, were unknown and were estimated through a process of manual calibration. Firstly, an exercise was undertaken whereby a parameter value for the probability of VZV infection given contact was applied to the model and the modelled varicella incidence data were recorded and compared with observed incidence data. This process was repeated using different parameter values until the modelled varicella incidence data approximated observed incidence data. The parameter value was then fixed in the model. Secondly, taking each of the 16 age-specific herpes zoster reactivation rate parameters in turn (from youngest to oldest), a parameter value was applied to the model and the modelled age-specific herpes zoster incidence data were recorded. As above, the process was repeated using different parameter values until the modelled incidence data approximated the observed data. The parameter value for that age group was then fixed in the model. Lastly, the process was repeated for each of the age-specific herpes zoster reactivation rate parameters in turn until all 16 values were estimated and fixed in the model.

Appendix A 5.2 Differential equations for epidemiological model

Age Group 1 (before vaccination)

$$dS_1/dt = bN - \lambda_1 S_1 - \alpha_1 S_1 - \mu_1 S_1 \ , \qquad where\ \lambda_1 = \sum_{j=1}^{16} pc_{1j}\left(I_j/N_j\right)$$

$$dE_1/dt = \lambda_1 S_1 - \sigma E_1 - \alpha_1 E_1 - \mu_1 E_1$$

$$dI_1/dt = \sigma E_1 - \gamma I_1 - \alpha_1 I_1 - \mu_1 I_1$$

$$dR_1/dt = \gamma I_1 - \delta R_1 + g_1\lambda_1 SZ_1 - \alpha_1 R_1 - \mu_1 R_1$$

$$dSZ_1/dt = \delta R_1 - \rho_1 SZ_1 - g_1\lambda_1 SZ_1 - \alpha_1 SZ_1 - \mu_1 SZ_1$$

$$dIZ_1/dt = \rho_1 SZ_1 - \gamma_z IZ_1 - \alpha_1 IZ_1 - \mu_1 IZ_1$$

$$dRZ_1/dt = \gamma_z IZ_1 - \alpha_1 RZ_1 - \mu_1 RZ_1$$

$$dD_1/dt = \mu_1 S_1 + \mu_1 E_1 + \mu_1 I_1 + \mu_1 R_1 + \mu_1 SZ_1 + \mu_1 IZ_1 + \mu_1 RZ_1$$

Age Group 2 (assumed first dose vaccination)

$$dS_2/dt = \alpha_1 S_1 - cv1*(1-vf1)*ve1*a_1 S_1 - cv1*(1-vf1)*(1-ve1)*a_1 S_1 - cv1*vf1*a_1 S_1 - \lambda_2*(1-cv1)*a_1 S_1 - \lambda_2 S_2 - \alpha_2 S_2 - \mu_2 S_2 \ , \qquad where\ \lambda_2 = \sum_{j=1}^{16} pc_{2j}\left(I_j/N_j\right)$$

$$dE_2/dt = \alpha_1 E_1 + \lambda_2*(1-cv1)*a_1 S_1 + \lambda_2 VFS_2 + \lambda_2 S_2 - \sigma E_2 - \alpha_2 E_2 - \mu_2 E_2$$

$$dI_2/dt = \alpha_1 I_1 + \sigma E_2 - \gamma I_2 - \alpha_2 I_2 - \mu_2 I_2$$

$$dR_2/dt = \alpha_1 R_1 + \gamma I_2 - \delta R_2 + g_2\lambda_2 SZ_2 - \alpha_2 R_2 - \mu_2 R_2$$

$$dSZ_2/dt = \alpha_1 SZ_1 + \delta R_2 - \rho_2 SZ_2 - g_2\lambda_2 SZ_2 - \alpha_2 SZ_2 - \mu_2 SZ_2$$

$$dIZ_2/dt = \alpha_1 IZ_1 + \rho_2 SZ_2 - \gamma_z IZ_2 - \alpha_2 IZ_2 - \mu_2 IZ_2$$

$$dRZ_2/dt = \alpha_1 RZ_1 + \gamma_z IZ_2 - \alpha_2 RZ_2 - \mu_2 RZ_2$$

$$dV1P_2/dt = cv1*(1-vf1)*ve1*a_1 S_1 - w1*V1P_2 - \alpha_2 V1P_2 - \mu_2 V1P_2$$

$$dVFS_2/dt = cv1*vf1*a_1 S_1 - \lambda_2 VFS_2 - \alpha_2 VFS_2 - \mu_2 VFS_2$$

$$dVS_2/dt = cv1*(1-vf1)*(1-ve1)*a_1 S_1 + w1*V1P_2 - v\lambda_2 VS_2 - \alpha_2 VS_2 - \mu_2 VS_2$$

$$dVE_2/dt = v\lambda_2 VS_2 - \sigma VE_2 - \alpha_2 VE_2 - \mu_2 VE_2$$

$$dVI_2/dt = \sigma VE_2 - \gamma VI_2 - \alpha_2 VI_2 - \mu_2 VI_2$$

$$dVR_2/dt = \gamma VI_2 - \delta VR_2 + g_2\lambda_2 VSZ_2 - \alpha_2 VR_2 - \mu_2 VR_2$$

$$dVSZ_2/dt = \delta VR_2 - v\rho_2 VSZ_2 - g_2\lambda_2 VSZ_2 - \alpha_2 VSZ_2 - \mu_2 VSZ_2$$

$$dVIZ_2/dt = v\rho_2 VSZ_2 - \gamma_z VIZ_2 - \alpha_2 VIZ_2 - \mu_2 VIZ_2$$

$$dVRZ_2/dt = \gamma_z VIZ_2 - \alpha_2 VRZ_2 - \mu_2 VRZ_2$$

$dD_2/dt = \mu_2 S_2 + \mu_2 E_2 + \mu_2 I_2 + \mu_2 R_2 + \mu_2 V1P_2 + \mu_2 VFS_2 + \mu_2 VS_2 + \mu_2 VE_2 + \mu_2 VI_2 + \mu_2 VR_2 + \mu_2 SZ_2 + \mu_2 IZ_2 + \mu_2 RZ_2$

$dVD_2/dt = \mu_2 V1P_2 + \mu_2 VFS_2 + \mu_2 VS_2 + \mu_2 VE_2 + \mu_2 VI_2 + \mu_2 VR_2 + \mu_2 VSZ_2 + \mu_2 VIZ_2 + \mu_2 VRZ_2$

Age Group 3 (assumed second dose vaccination)

$dS_3/dt = \alpha_2 S_2 - \lambda_3 S_3 - \alpha_3 S_3 - \mu_3 S_3$, $\quad where\ \lambda_3 = \sum_{j=1}^{16} pc_{3j}\left(I_j/N_j\right)$

$dE_3/dt = \alpha_2 E_2 + \lambda_3 S_3 + \lambda_3 VFS_3 - \sigma E_3 - \alpha_3 E_3 - \mu_3 E_3$

$dI_3/dt = \alpha_2 I_2 + \sigma E_3 - \gamma I_3 - \alpha_3 I_3 - \mu_3 I_3$

$dR_3/dt = \alpha_2 R_2 + \gamma I_3 - \delta R_3 + g_3 \lambda_3 SZ_3 - \alpha_3 R_3 - \mu_3 R_3$

$dSZ_3/dt = \alpha_2 SZ_2 + \delta R_3 - \rho_3 SZ_3 - g_3 \lambda_3 SZ_3 - \alpha_3 SZ_3 - \mu_3 SZ_3$

$dIZ_3/dt = \alpha_2 IZ_2 + \rho_3 SZ_3 - \gamma_z IZ_3 - \alpha_3 IZ_3 - \mu_3 IZ_3$

$dRZ_3/dt = \alpha_2 RZ_2 + \gamma_z IZ_3 - \alpha_3 RZ_3 - \mu_3 RZ_3$

$dV1P_3/dt = a_2 V1P_2 - cv2 * (1 - vf2) * a_2 VIP_2 - w1 * V1P_3 - \alpha_3 V1P_3 - \mu_3 V1P_3$

$dV1Q_3/dt = cv2 * (1 - vf2) * ve1 * a_2 VFS_2 - w1 * V1Q_3 - \alpha_3 V1Q_3 - \mu_3 V1Q_3$

$dV2P_3/dt = cv2 * (1 - vf2) * a_2 VIP_2 + cv2 * (1 - vf2) * ve2 * a_2 VS_2 - \alpha_3 V2P_3 - \mu_2 V2P_3$

$dVFS_3/dt = a_2 VFS_2 - cv2 * (1 - vf2) * ve1 * a_2 VFS_2 - cv2 * (1 - vf2) * (1 - ve1) * a_2 VFS_2 - \lambda_3 VFS_3 - \alpha_3 VFS_3 - \mu_3 VFS_3$

$dVS_3/dt = a_2 VS_2 - cv2 * (1 - vf2) * ve2 * a_2 VS_2 + cv2 * (1 - vf2) * (1 - ve1) * a_2 VFS_2 + w1 * V1P_3 + w1 * V1Q_3 - v\lambda_3 VS_3 - \alpha_3 VS_3 - \mu_3 VS_3$

$dVE_3/dt = \alpha_2 VE_2 + v\lambda_3 VS_3 - \sigma VE_3 - \alpha_3 VE_3 - \mu_3 VE_3$

$dVI_3/dt = \alpha_2 VI_2 + \sigma VE_3 - \gamma VI_3 - \alpha_3 VI_3 - \mu_3 VI_3$

$dVR_3/dt = \alpha_2 VR_2 + \gamma VI_3 - \delta VR_3 + g_3 \lambda_3 VSZ_3 - \alpha_3 VR_3 - \mu_3 VR_3$

$dVSZ_3/dt = \alpha_2 VSZ_2 + \delta VR_3 - v\rho_3 VSZ_3 - g_3 \lambda_3 VSZ_3 - \alpha_3 VSZ_3 - \mu_3 VSZ_3$

$dVIZ_3/dt = \alpha_2 VIZ_2 + v\rho_3 VSZ_3 - \gamma_z VIZ_3 - \alpha_3 VIZ_3 - \mu_3 VIZ_3$

$dVRZ_3/dt = \alpha_2 VRZ_2 + \gamma_z VIZ_3 - \alpha_3 VRZ_3 - \mu_3 VRZ_3$

$dD_3/dt = \mu_3 S_3 + \mu_3 E_3 + \mu_3 I_3 + \mu_3 R_3 + \mu_3 SZ_3 + \mu_3 IZ + \mu_3 RZ_3$

$dVD_3/dt = \mu_3 V1P_3 + \mu_3 V1Q_3 + \mu_3 V2P_3 + \mu_3 VFS_3 + \mu_3 VS_3 + \mu_3 VE_3 + \mu_3 VI_3 + \mu_3 VR_3 + \mu_3 VSZ_3 + \mu_3 VIZ + \mu_3 VRZ_3$

Age Groups after vaccination (excluding final age group)

$dS_i/dt = \alpha_{i-1} S_{i-1} - \lambda_i S_i - \alpha_i S_i - \mu_i S_i$, $\quad where\ \lambda_i = \sum_{j=1}^{16} pc_{ij}\left(I_j/N_j\right)$

$dE_i/dt = \alpha_{i-1} E_{i-1} + \lambda_i S_i + \lambda_i VFS_i - \sigma_i E_i - \alpha_i E_i - \mu_i E_i$

$dI_i/dt = \alpha_{i-1} I_{i-1} + \sigma_i E_i - \gamma_i I_i - \alpha_i I_i - \mu_i I_i$

$dR_i/dt = \alpha_{i-1} R_{i-1} + \gamma_i I_i - \delta R_i + g_i \lambda_i SZ_i - \alpha_i R_i - \mu_i R_i$

$$dSZ_i/dt = \alpha_{i-1}SZ_{i-1} + \delta R_i - \rho_i SZ_i - g_i\lambda_i SZ_i - \alpha_i SZ_i - \mu_i SZ_i$$
$$dIZ_i/dt = \alpha_{i-1}IZ_{i-1} + \rho_i SZ_i - \gamma_z IZ_i - \alpha_i IZ_i - \mu_i IZ_i$$
$$dRZ_i/dt = \alpha_{i-1}RZ_{i-1} + \gamma_z IZ_i - \alpha_i RZ_i - \mu_i RZ_i$$
$$dV1P_i/dt = a_{i-1}V1P_{i-1} - w1 * V1P_i - \alpha_i V1P_i - \mu_i V1P_i$$
$$dV1Q_i/dt = a_{i-1}V1Q_{i-1} - w1 * V1Q_i - \alpha_i V1Q_i - \mu_i V1Q_i$$
$$dV2P_i/dt = a_{i-1}V2P_{i-1} - \alpha_i V2P_i - \mu_i V2P_i$$
$$dVFS_i/dt = a_{i-1}VFS_{i-1} - \lambda_i VFS_i - \alpha_i VFS_i - \mu_i VFS_i$$
$$dVS_i/dt = a_{i-1}VS_{i-1} + w1 * V1P_i + w1 * V1Q_i + w1 * V2P_i - v\lambda_i VS_i - \alpha_i VS_i - \mu_i VS_i$$
$$dVE_i/dt = \alpha_{i-1}VE_{i-1} + v\lambda_i VS_i - \sigma VE_i - \alpha_i VE_i - \mu_i VE_i$$
$$dVI_i/dt = \alpha_{i-1}VI_{i-1} + \sigma VE_i - \gamma VI_i - \alpha_i VI_i - \gamma VI_i$$
$$dVR_i/dt = \alpha_{i-1}VR_{i-1} + \gamma VI_i - \delta VR_i + g_i\lambda_i VSZ_i - \alpha_i VR_i - \mu_i VR_i$$
$$dVSZ_i/dt = \alpha_{i-1}VSZ_{i-1} + \delta VR_i - v\rho_i VSZ_i - g_i\lambda_i VSZ_i - \alpha_i VSZ_i - \mu_i VSZ_i$$
$$dVIZ_i/dt = \alpha_{i-1}VIZ_{i-1} + v\rho_i VSZ_i - \gamma_z VIZ_i - \alpha_i VIZ_i - \mu_i VIZ_i$$
$$dVRZ_i/dt = \alpha_{i-1}VRZ_{i-1} + \gamma_z VIZ_i - \alpha_i VRZ_i - \mu_i VRZ_i$$
$$dD_i/dt = \mu_i S_i + \mu_i E_i + \mu_i I_i + \mu_i R_i + \mu_i SZ_i + \mu_i IZ_i + \mu_i RZ_i$$
$$dVD_i/dt = \mu_i V1P_i + \mu_i V1Q_i + \mu_i V2P_i + \mu_i VFS_i + \mu_i VS_i + \mu_i VE_i + \mu_i VI_i + \mu_i VR_i + \mu_i VSZ_i + \mu_i VIZ_i + \mu_i VRZ_i$$

Final age group (no ageing)

$$dS_i/dt = \alpha_{i-1}S_{i-1} - \lambda_i S_i - \mu_i S_i \ ,$$

$$where\ \lambda_i = \sum_{j=1}^{16} pc_{ij}\left(I_j/N_j\right)$$

$$dE_i/dt = \alpha_{i-1}E_{i-1} + \lambda_i S_i + \lambda_i VFS_i - \sigma E_i - \mu_i E_i$$
$$dI_i/dt = \alpha_{i-1}I_{i-1} + \sigma E_i - \gamma I_i - \mu_i I_i$$
$$dR_i/dt = \alpha_{i-1}R_{i-1} + \gamma I_i - \delta R_i + g_i\lambda_i SZ_i - \mu_i R_i$$
$$dSZ_i/dt = \alpha_{i-1}SZ_{i-1} + \delta R_i - \rho_i SZ_i - g_i\lambda_i SZ_i - \mu_i SZ_i$$
$$dIZ_i/dt = \alpha_{i-1}IZ_{i-1} + \rho_i SZ_i - \gamma_z IZ_i - \mu_i IZ_i$$
$$dRZ_i/dt = \alpha_{i-1}RZ_{i-1} + \gamma_z IZ_i - \mu_i RZ_i$$
$$dV1P_i/dt = a_{i-1}V1P_{i-1} - w1 * V1P_i - \mu_i V1P_i$$
$$dV1Q_i/dt = a_{i-1}V1Q_{i-1} - w1 * V1Q_i - \mu_i V1Q_i$$
$$dV2P_i/dt = a_{i-1}V2P_{i-1} - \mu_i V2P_i$$
$$dVFS_i/dt = a_{i-1}VFS_{i-1} - \lambda_i VFS_i - \mu_i VFS_i$$

$$dVS_i/dt = \alpha_{i-1}VS_{i-1} + w1 * V1P_i + w1 * V1Q_i - v\lambda_i VS_i - \mu_i VS_i$$
$$dVE_i/dt = \alpha_{i-1}VE_{i-1} + v\lambda_i VS_i - \sigma VE_i - \mu_i VE_i$$
$$dVI_i/dt = \alpha_{i-1}VI_{i-1} + \sigma VE_x - \gamma VI_i - \mu_i VI_i$$
$$dVR_i/dt = \alpha_{i-1}VR_{i-1} + \gamma VI_i - \delta VR_i + g_i\lambda_i VSZ_i - \mu_i VR_i$$
$$dVSZ_i/dt = \alpha_{i-1}VSZ_{i-1} + \delta VR_i - v\rho_i VSZ_i - g_i\lambda_i VSZ_i - \mu_i VSZ_i$$
$$dVIZ_i/dt = \alpha_{i-1}VIZ_{i-1} + v\rho_i VSZ_i - \gamma_z VIZ_i - \mu_i VIZ_i$$
$$dVRZ_i/dt = \alpha_{i-1}VRZ_{i-1} + \gamma_z VIZ_i - \mu_i VRZ_i$$
$$dD_i/dt = \mu_i S_i + \mu_i E_i + \mu_i I_i + \mu_i R_i + \mu_i V1P_i + \mu_i SZ_i + \mu_i IZ_i + \mu_i RZ_i$$
$$dVD_i/dt = \mu_i V1P_i + \mu_i V1Q_i + \mu_i V2P_i + \mu_i VFS_i + \mu_i VS_i + \mu_i VE_i + \mu_i VI_i + \mu_i VR_i + \mu_i VSZ_i + \mu_i VIZ_i + \mu_i VRZ_i$$

Key for health states:

D – dead due to all causes; E – exposed; I – infectious; IZ – infected with zoster; R – recovered; RZ – recovered from zoster; S – susceptible; SZ – susceptible to zoster; VD – vaccinated and dead due to all causes; VE – vaccinated exposed; VFS – vaccinated failed susceptible; VI – vaccinated infectious; VI – vaccinated infected with zoster; V1P – vaccinated protected with one dose (after one dose); V1Q – vaccinated protected with one dose (after two doses); VR – vaccinated recovered; VRZ – vaccinated recovered from zoster; VS – vaccinated susceptible; VSZ – vaccinated susceptible to zoster; V2P – vaccinated protected with two doses (after two doses);.

Key for rates:

α - ageing rate; b - birth rate; cv1/2 - coverage rate 1-dose/2-dose; δ - waning rate from recovered varicella to susceptible to herpes zoster; g(a)λ(a) - exogenous boosting rate against herpes zoster by age; h – relative varicella zoster virus reactivation after vaccination; λ(a) - force of varicella zoster virus infection by age; μ - all-cause mortality rate; ρ(a) - reactivation rate of infectious herpes zoster by age; σ - incubation rate for varicella; vλ(a) - force of varicella zoster virus infection in those vaccinated by age; ve1/2 - vaccine effectiveness 1st/2nd dose; vf1/2 - vaccine failure 1st/2nd dose; w1 - waning rate 1-dose; γ_v - recovery rate from varicella; γ_z - recovery rate from zoster.

Appendix A 5.3 Costing methods

In accordance with national HTA guidelines in Ireland, all costs are presented in 2022 Irish Euro (€).[130]

Payer perspective - varicella

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.[309, 310] 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 A 5.1**).[311] The opportunity cost of a GP visit using a GP visit or medical card was sourced from the literature,[252] inflated to 2022 Irish € (using the *Doctor's fees* sub index of the CSO's Consumer Price Index [CPI] monthly series data)[312] and estimated at €49.72.

Table A 5.1 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[311]	Proportion of population with a medical card[311]
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%

Age group	Proportion of population eligible for a GP visit card or with a medical card[311]	Proportion of population with a medical card[311]
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 A 5.2**) was estimated based on the total number of HIPE discharges with a primary diagnosis of varicella. 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 Healthcare Pricing Office (HPO).[250] 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 A 5.2** are estimated average costs and individual cases could incur higher or lower costs depending on the intensity of treatment and length of stay.

Table A 5.2 Estimated average hospitalisation cost for a case of severe varicella

Age group	Estimated average hospitalisation cost for a case of severe varicella[249, 250]
<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
10 to 19	€3,797
20 to 39	€4,451
40 to 59	€5,484
60 to 79	€7,714
≥80 years	€7,455

Payer perspective – herpes zoster

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. 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,[244] 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);[312] 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 A 5.3**) was estimated based on the total number of HIPE discharges with a primary diagnosis of herpes zoster. 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.[250] 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 A 5.3** are estimated average costs and individual cases could incur higher or lower costs depending on the intensity of treatment and length of stay.

Table A 5.3 Estimated average hospitalisation cost for a case of severe herpes zoster

Age group	Estimated average hospitalisation cost for a case of severe herpes zoster[249, 250]
0 to 9 years	€4,598
10 to 19	€5,207
20 to 29	€5,280
30 to 39	€5,826
40 to 49	€5,574
49 to 59	€5,064
60 to 69	€5,512
70 to 79	€5,344
≥80 years	€5,236

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.[311] The cost of a GP visit for private patients was sourced from the literature,[252] inflated to 2022 Irish € (using the *Doctor's fees* sub index of the CSO's Consumer Price Index [CPI] monthly series data)[312] 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.[313] 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 A 5.4**).[314] Earnings analysis data published by the CSO[251] were used to estimate median daily earnings (in 2022) by age group (**Table A 5.4**). 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.[249]

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[315] 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.[249]

Table A 5.4 Proportion of the population working and estimate of daily lost productivity to society by age group

Age group	Proportion of the population working[314]	Estimate of median daily earnings[251]
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
60 to 69 years	42.09%	€119.79
70 to 79 years	1.33%	€119.79

Appendix A 5.4 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[29]
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[311] Health Service Executive[309, 310]
Probability GP visit public_age group 2	100%	100%	100%	
Probability GP visit public_age group 3	100%	100%	100%	
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[311]
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%	

Parameter Description	Base case value	Lower bound	Upper bound	Source
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				
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 In-Patient Enquiry (HIPE) System Discharge Data[249]
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%	

Parameter Description	Base case value	Lower bound	Upper bound	Source
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.[243]
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 In-Patient Enquiry (HIPE) System Discharge Data[249]
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%	
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%	

Parameter Description	Base case value	Lower bound	Upper bound	Source
Direct medical costs - varicella				
Cost of GP visit for varicella_public	€49.72	€39.78	€59.66	Smith et al.[252] Lower and upper bounds +/-20%.
Cost of GP visit for varicella_private	€54.05	€43.24	€64.86	
Cost of OTC medication for varicella_age groups 1-3	€13.90	€11.12	€16.68	Calculated. Lower and upper bounds +/-20%.
Cost of OTC medication for varicella_age groups 4-8	€17.90	€14.32	€21.48	
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 In-Patient Enquiry (HIPE) System Discharge Data[249] and Activity Based Funding Admitted Patient Price List.[250] 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.[244] Lower and upper bounds +/-20%.
Cost of GP for PHN	€94.23	€75.38	€113.08	
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.[244] Lower and upper bounds +/-20%.
Cost of prescription medication for PHN	€101.88	€81.50	€122.26	
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 In-Patient Enquiry (HIPE) System Discharge Data[249] and Activity Based Funding Admitted Patient Price List.[250] 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.[314] 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)[315]
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%	

Parameter Description	Base case value	Lower bound	Upper bound	Source
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%	
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.[314] 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.[314] 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%	

Parameter Description	Base case value	Lower bound	Upper bound	Source
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)[315]
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)[315]
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%	
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%	

Parameter Description	Base case value	Lower bound	Upper bound	Source
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[251] 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[251] 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	€0.00	€0.00	€0.00	

Parameter Description	Base case value	Lower bound	Upper bound	Source
PHN_age group 10				
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	
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 In-Patient Enquiry (HIPE) System Discharge Data.[249]
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	

Parameter Description	Base case value	Lower bound	Upper bound	Source
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 In-Patient Enquiry (HIPE) System Discharge Data.[249]
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.[246]
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.[247]
QALY loss acute herpes zoster_age groups 15-16	0.0120	0.0070	0.0180	
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[231]

Parameter Description	Base case value	Lower bound	Upper bound	Source
Coverage 1st dose	88.0%	83.1%	93.0%	Health Protection Surveillance Centre[239] (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[239, 240] (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[316]
Cost of varicella vaccine - dose one	€32.73	€26.18	€39.28	Akpo et al.[213] (€ 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.[253] 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.[254]
Education and Communication cost as a proportion of vaccine procurement cost	1.5%	40.0%	4.4%	
Value Added Tax (VAT)	23%	23%	23%	Revenue Irish Tax and Customs.[317]
Probability of mild adverse event with varicella vaccine	27.0%	10.0%	50.0%	WHO.[245] 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.[130]
Annual discount rate - outcomes (%)	4.0%	0.0%	10.0%	

Appendix A 5.5 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.[225] However, the pathophysiology of exogenous boosting is poorly understood, much debated and the magnitude of the effect, if it exists, is unknown.[225] In countries with long-standing universal varicella vaccination programmes, large increases in incidence of herpes zoster have not been observed since the introduction of the vaccination programme.[274, 318] Furthermore, a recent modelling study exploring alternative forms of exogenous boosting concluded that strong protection from exogenous boosting may not necessarily lead to a surge in incidence of herpes zoster after the introduction of a universal varicella vaccination programme.[318] Therefore in this economic evaluation, conducted to inform health policy decision-making, an assumption of full exogenous boosting was deemed to be a conservative approach to adopt. The conservative approach enables health policy decision makers to understand the 'worst case' impact of the assumption on the cost effectiveness of the intervention.

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 A 5.5**). In terms of cost effectiveness, the one-dose strategy remained cost effective, relative to no vaccination, at a WTP threshold of €20,000 per 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 per QALY gained at €68,966 per 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 per QALY gained, at €65,214 per QALY gained.

Table A 5.5 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. The ICER for the two-dose long interval strategy, relative to the one-dose strategy, was €107,326 per QALY gained and for the two-dose short interval strategy, relative to the long interval strategy, was €59,918 per 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 per QALY gained (ICER of €10,806 per QALY gained). The ICER for the two-dose long interval strategy, relative to the one-dose strategy, increased to €51,788 per QALY gained and that for the two-dose short interval strategy, relative to the long interval strategy, was €45,200 per 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 per QALY gained (ICER of €13,687 per QALY gained). The ICER for the two-dose long interval strategy, relative to the one-dose strategy, increased to €61,001 per QALY gained and that for the two-dose short interval strategy, relative to the long interval strategy, was €53,574 per 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 per QALY gained. The ICERs for the two-dose long interval strategy, relative to the one-dose strategy, ranged from €45,383 per QALY gained (when the GP administration cost was set at €25.00), to €45,940 per 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 per QALY gained and ranged from €68,188 per QALY gained (when the GP administration cost was set at €25.00), to €123,631 per 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 per QALY gained, with ICERs of €40,732 and €36,125 per QALY gained respectively. The results for all scenarios are presented in **Table A 5.6**.

Table A 5.6 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	€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-	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	€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	€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	€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	€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	€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	€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.

Appendix A 5.6 Probabilistic sensitivity analysis results

Figure A 5.1 Cost-effectiveness plane of one-dose varicella vaccination strategy versus no-vaccination (from the payer perspective)

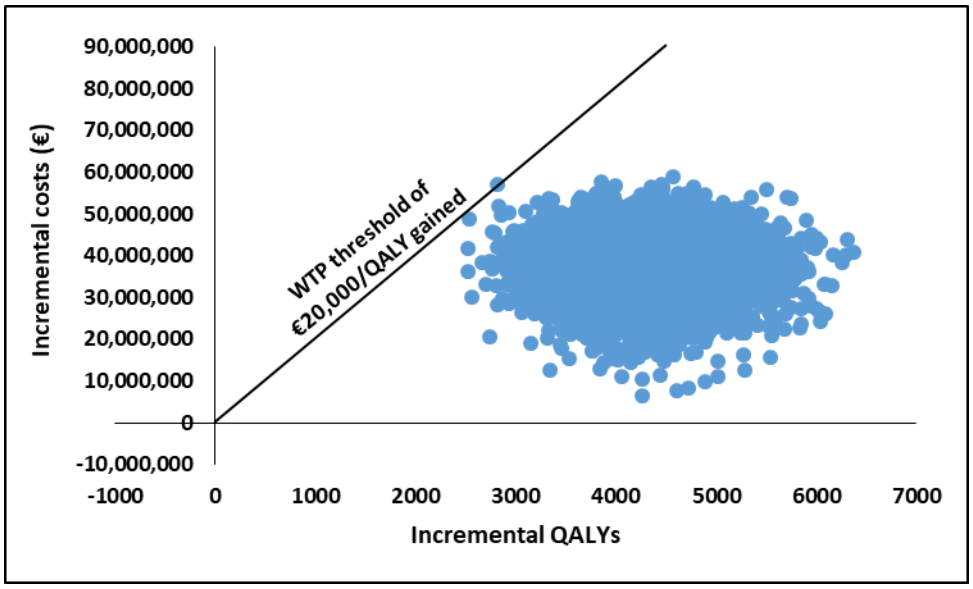


Figure A 5.2 Cost-effectiveness plane of two-dose long interval versus one-dose varicella vaccination strategy (from the payer perspective)

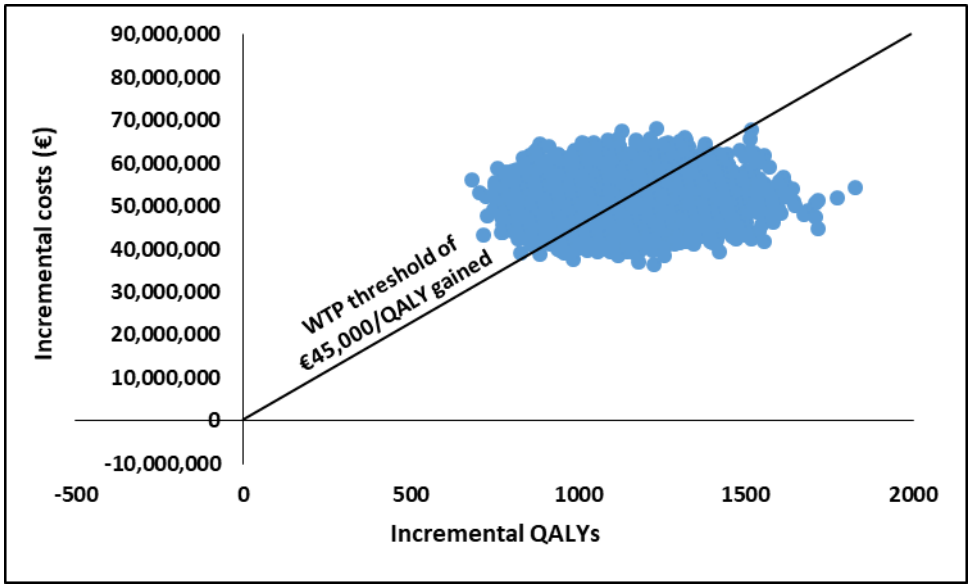


Figure A 5.3 Cost-effectiveness plane of two-dose short interval versus two-dose long interval varicella vaccination strategy (from the payer perspective)

