Varicella in the Netherlands

Background information for the
Health Council

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Colophon

Synopsis

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Varicella (chickenpox) is a disease caused by infection with the varicella-zoster virus (VZV). After someone has contracted varicella, the virus remains in the body without being active. If, at a later stage, the virus becomes active again, it can cause herpes zoster (shingles).

In the Netherlands, the Minister of Health, Welfare and Sport determines which vaccinations are offered through the National Immunisation Programme, basing his or her decision on the advice of the Health Council. The Health Council is now preparing its advice on vaccinating against varicella.

To support the Health Council's advice, the RIVM has gathered background information on vaccination against varicella. This overview provides, among other things, information on the number of people in the Netherlands who fall ill each year, the efficacy and safety of vaccines, and the public's opinion on varicella vaccination.

Varicella usually starts with mild fever and lethargy (in children). After 1 or 2 days, small vesicles appear on the body, starting on the head or torso. These vesicles develop into blisters that cause itching and then dry out into crusts after a few days. The symptoms last about a week.

Varicella is usually mild. It can sometimes cause serious complications, such as central nervous system manifestations, pneumonia or bacterial infections. People rarely die from varicella. Almost everyone in the Netherlands contracts varicella sooner or later; it is most common, however, in children under 5 years of age.

Keywords: varicella, chickenpox, vaccination, disease burden, cost-effectiveness, safety, acceptance

Publiekssamenvatting

Waterpokken in Nederland
Achtergrondinformatie voor de Gezondheidsraad

Waterpokken is een ziekte die wordt veroorzaakt door een infectie met het varicellazostervirus (VZV). Nadat iemand waterpokken heeft gekregen, blijft het virus in het lichaam achter zonder actief te zijn. Als het virus later weer actief wordt, kan het gordelroos veroorzaken.

In Nederland bepaalt de minister van Volksgezondheid, Welzijn en Sport (VWS) welke vaccinaties via het Rijksvaccinatieprogramma worden aangeboden. De minister neemt die beslissing op basis van een advies van de Gezondheidsraad. De Gezondheidsraad bereidt nu een advies voor over vaccinatie tegen waterpokken.

Als ondersteuning van het advies door de Gezondheidsraad heeft het RIVM achtergrondinformatie verzameld over vaccinatie tegen waterpokken. Dit overzicht biedt onder meer informatie over het aantal mensen in Nederland dat per jaar ziek wordt, de werkzaamheid en veiligheid van vaccins en de mening van het publiek over waterpokkenvaccinatie.

Waterpokken begint meestal met lichte koorts en hangerigheid (bij kinderen). Na 1 of 2 dagen ontstaan kleine bultjes op het lichaam, beginnend op het hoofd of de romp. Deze bultjes ontwikkelen zich tot blaasjes die jeuk veroorzaken en na een paar dagen tot korstjes indrogen. De ziekteverschijnselen duren ongeveer een week.

Waterpokken verloopt meestal mild. Soms kan het ernstige complicaties veroorzaken, bijvoorbeeld aantasting van het centrale zenuwstelsel, longontsteking, of bacteriële infecties. Mensen overlijden bijna nooit aan waterpokken. Bijna iedereen in Nederland krijgt vroeg of laat de waterpokken; het komt het meest voor bij kinderen onder de 5 jaar.

Kernwoorden: varicella, waterpokken, vaccinatie, ziektelast, kosteneffectiviteit, veiligheid, acceptatie

Contents

1 Background

Varicella is caused by the varicella-zoster virus (VZV). Primary infection leads to varicella (also called chickenpox), whereas herpes zoster (also called shingles) is caused by reactivation of latent VZV in sensory nerve ganglia. In contrast to herpes zoster, which predominantly affects adults aged 50 years and older, varicella is mainly a childhood disease [1, 2]. In the Netherlands, nearly everyone is affected by VZV at a young age; at 6 years of age more than 95% of the population is already seropositive [3]. Varicella is characterised by a vesicular dermatomal rash, usually accompanied by fever and malaise. Varicella normally results in mild to moderate illness, but serious complications (e.g. central nervous system manifestations, pneumonia, secondary bacterial infections) and death do occur. Therefore, prevention by vaccination might be valuable.

In 2007, the Health Council of the Netherlands judged that it was unclear whether the severity and extent of the disease burden of varicella in the Netherlands was considerable enough to introduce varicella vaccination. The Health Council recommended a further review of the importance and urgency of vaccination against varicella once more information on the national disease burden became available [4]. Such information would primarily provide insight into complications and mortality due to varicella, which might have been underestimated. An important aspect of the Health Council's deliberation was that it was not yet clear how varicella vaccination intervenes in the dynamic balance between varicella and herpes zoster (i.e. it is possible that herpes zoster incidence would temporarily increase as a result of varicella vaccination).

Since 2007, more information regarding the severity and disease burden of varicella in the Netherlands has become available. Experience with varicella vaccination in other countries has provided additional insight. Given the availability of this new information, there is a need to reconsider whether or not vaccination against varicella is desirable in the Netherlands.

In this report, we present the most recent scientific information available on varicella in general; on the burden of varicella in the Netherlands; on the effectiveness, safety, acceptance, and cost-effectiveness of available vaccines against varicella; and on the implementation of varicella vaccination. We have structured the report according to the criteria laid down by the Health Council of the Netherlands for the assessment of vaccinations [5].

2 Varicella

2.1 Pathogen

Varicella is caused by the varicella-zoster virus (VZV), an exclusively human pathogen. This alpha herpesvirus has a very stable genome and a low mutation rate. Primary infection with VZV manifests clinically as varicella, usually in childhood. Subsequently, the virus persists in sensory nerve ganglia, establishing latent infection in neuronal cells. After endogenous reactivation, the virus can spread unilaterally along a dermatome to cause herpes zoster, most common in older adults [1, 2].

2.2 Transmission

VZV is highly contagious and is transmitted by air as droplets spread from the oropharynx or from aerosols from skin lesions of a person with varicella or herpes zoster [2]. Primary varicella has a striking seasonal pattern: the peak incidence normally occurs in winter and early spring, or in the cooler, drier months in the tropics. Periodic large outbreaks occur with an inter-epidemic cycle of 2–5 years [6, 7].

The latency mechanism of VZV is not fully understood. The recently discovered VZV latency-associated transcript (VLT) may function to maintain latency by repressing the transcription of *ORF61* during lytic infections [8, 9]. The reactivation of VZV is thought to result from waning cell-mediated immunity (VZV-CMI) and not from waning VZV-specific antibodies over time [2]. Hope-Simpson hypothesised that the immune system of a person who has had varicella is 'boosted' in two different ways: 1) by exogenous boosting, i.e. through contact with an infectious varicella (or herpes zoster) case and 2) by endogenous boosting, i.e. through subclinical reactivation of VZV. The development of herpes zoster might be postponed through both types of immune boosting [10]. This may have implications for universal varicella vaccination: due to diminished VZV circulation (less exogenous boosting), herpes zoster incidence might temporarily increase [11]. While exogenous boosting may exist, its magnitude is currently unknown [12, 13].

2.3 Symptoms and outcomes

Varicella usually starts with a mild fever and malaise. After 1–2 days, a pruritic, vesicular rash develops on the body, beginning on the head or trunk. These lesions progress through different stages (macular, papular, vesicular and pustular) before they begin to crust. Lesions are typically present at all stages of development at the same time. Varicella usually results in mild to moderate disease characterised by systemic signs and symptoms (e.g. fever, headache, malaise and loss of appetite or feeding difficulties). Illness usually persists for 5–7 days [1, 6, 14].

Sometimes, varicella causes serious complications such as central nervous system manifestations, secondary bacterial infections and death. Secondary bacterial infections of the skin and underlying soft tissue occur most frequently and are more common in children. Invasive infections can be life-threatening (e.g. pneumonia, arthritis, osteomyelitis, necrotising

fasciitis and sepsis). Central nervous system manifestations can range from benign cerebellar ataxia to meningoencephalitis and meningitis. Varicella pneumonia, more common in adults, and haemorrhages are other serious complications [1, 14].

Varicella during pregnancy may lead to severe maternal and foetal disease. There is a risk of severe pneumonia and death for women who contract varicella in the last trimester of pregnancy. Severe maternal varicella at any stage of pregnancy may also cause intrauterine death. In children born to mothers who developed varicella during the first 20 weeks of gestation, congenital varicella syndrome occurs in 0.4–2% of cases. This syndrome manifests itself as various abnormalities, including large areas of skin scarring, hypoplastic limbs, chorioretinitis, cataracts and other eye and brain abnormalities. Neonatal varicella, which can develop if the mother contracts varicella during the last 3 weeks of pregnancy, is especially severe if the mother's rash appears between 5 days before and 2 days after delivery [1, 15].

Varicella in immunocompromised hosts is more likely to be severe than in healthy persons, with multi-organ system involvement. There is an increased risk that the virus will disseminate throughout the organs, new skin lesions will continue to appear for several weeks, vesicles will become large and haemorrhagic, and pneumonia or disseminated intravascular coagulation will develop [1, 7, 14].

2.4 Diagnostics

Diagnosis of varicella mostly occurs clinically. As the vesicular rash is characteristic of varicella, there is no need for laboratory confirmation in uncomplicated illness; this in contrast to complicated illness in the hospital setting. The second PIENTER serosurveillance study [3] showed a high positive (98.6%) and a low negative (43.0%) predicted value of self-reported varicella history in the Netherlands (Table 2.1; unpublished results). Among 0–5-year-olds the negative predictive value was considerably higher than among older age groups.

The use of polymerase chain reaction (PCR) to detect VZV in material from skin lesions is the most reliable method of confirming a diagnosis of varicella. Body fluids, such as saliva, blood, urine and cerebrospinal fluid, are less likely to provide an adequate sample. Other viral isolation techniques used to confirm varicella are direct immunofluorescence and viral culture, but these are generally not recommended because they are less sensitive than PCR or take more time. IgM serology testing is less sensitive than PCR testing of material from skin lesions and cannot discriminate between a primary infection (varicella) and reactivation (herpes zoster). IgG serology testing is used to asses immunity to varicella. The ELISA (enzyme-linked immunosorbent assay) for measurement of IgG antibodies is the major serological assay in commercial use [2].

Table 2.1 Self-reported varicella history by serologic immune status according to second PIENTER study conducted in 2006/2007 among people aged 0–79 years

Self-reported varicella history[a]	VZV-seropositive	VZV-seronegative	Total
Yes	[b] 3,672 (98.6%)	53 (1.4%)	3,725 (100%)
No	624 (57.0%)	[c] 471 (43.0%)	1,095 (100%)
Unknown	1,327 (97.3%)	37 (2.7%)	1,364 (100%)
Total	5,623 (90.9%)	561 (9.1%)	6,184 (100%)

[a] 'Have you ever experienced varicella?' [b] positive predictive value, [c] negative predictive value, VZV = varicella-zoster virus

2.5 Treatment

In general, varicella is a self-limiting disease. Treatment focuses on controlling fever, limiting pruritus and preventing dehydration. Antibiotics may be required for treatment of secondary bacterial infections. Patients at high risk of severe disease can be treated with antivirals (acyclovir or the prodrugs valaciclovir or famciclovir) [1]. This treatment is most effective if given within 24 hours of rash onset [16].

In people who are exposed to VZV and are at high risk of severe disease, passive immunisation with varicella zoster immunoglobulin (postexposure prophylaxis) can sometimes prevent or mitigate clinical varicella [1].

2.6 Risk factors

Nearly everyone in the Netherlands encounters the varicella-zoster virus (VZV) during early life, and natural infection normally induces lifelong immunity to clinical varicella.

The most important risk factors associated with *disease severity* are age, a compromised immune system and pregnancy. Very young infants, adults, and immunocompromised people are at increased risk of severe disease, hospitalisation and death. Furthermore, varicella during pregnancy may lead to severe maternal and foetal disease (see Section 2.3) [1, 7].

Although varicella is more severe in immunocompromised people, almost 90% of hospitalised patients with varicella are considered healthy or immunocompetent [1]. In the US (pre-vaccine era), the risk of hospitalisation for varicella pneumonia per 10,000 varicella cases was 20 times higher among adults than among children <5 years of age [17]. The risk of dying from varicella was 23–29 times higher in adults, and 4 times higher in infants, than in children [1].

3 Epidemiology of varicella

In countries with temperate climates, such as the Netherlands, varicella is mainly a childhood disease with a striking seasonal pattern, peak incidence occurring in winter and early spring. In tropical countries, the mean age of infection is considerably higher [1, 7]. In the Netherlands, nearly everyone is affected by the VZV at some time in their lives [3].

3.1 Surveillance of varicella in the Netherlands

In the Netherlands, varicella is not a notifiable disease. Therefore, estimates of the incidence and disease burden of varicella are based on seroepidemiological data (population-based PIENTER serosurveillance studies), primary care data from a large sentinel network of general practitioners belonging to the Netherlands institute for health services research (Nivel), national hospital discharge data from Dutch Hospital Data (DHD) and mortality data from Statistics Netherlands (CBS).

3.2 Seroepidemiology of VZV in the Netherlands

In the Netherlands, nearly everyone contracts varicella during early childhood (Figure 3.1). After the gradual waning of maternal antibodies from birth to the age of approximately 3.4 months, VZV seroprevalence increases rapidly with age: at 6 years of age more than 95% of the population is already seropositive [3, 18]. In the second PIENTER study (conducted in 2006/2007), the overall seroprevalence of VZV-specific antibodies among people aged 0-79 years was 94.6% (95% confidence interval (CI): 93.2–96.0%) [3]. This was similar to the 95.6% (95%CI: 94.9–96.3%) found in the first PIENTER study (conducted in 1995/1996) [19].
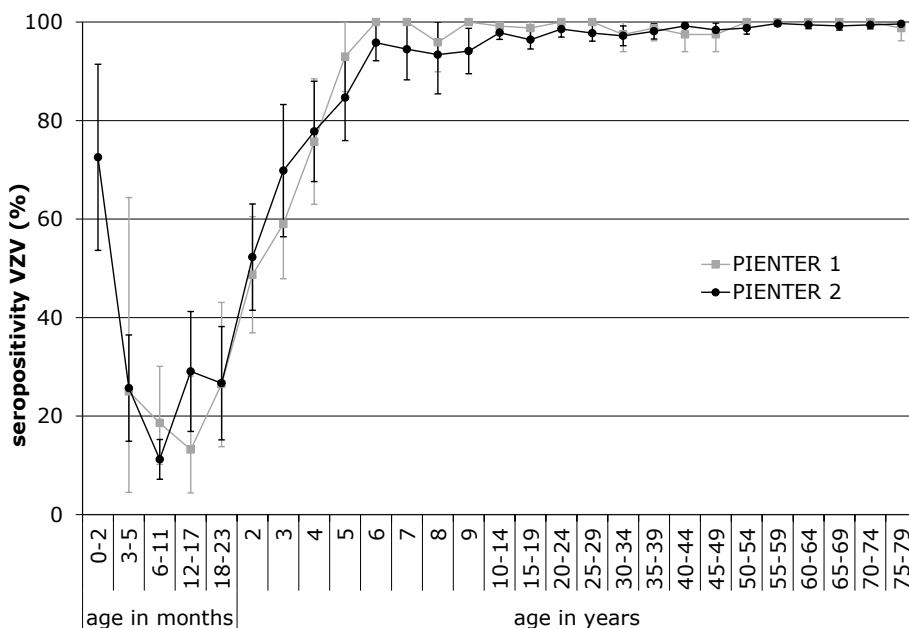

Figure 3.1 Age-specific seroprevalence for varicella-zoster virus (VZV)-specific antibodies, with 95% confidence intervals – PIENTER 2 (2006/2007) versus PIENTER 1 (1995/1996) [3, 19]

Among children younger than 6 years, determinants associated with a lower VZV seropositivity were: young age, first-generation non-Dutch ethnicity, and low frequency of attendance at a day care centre or nursery school [3].

Van Rijckevorsel et al. studied VZV seroprevalence in Amsterdam. They confirmed that ethnic background and first generation of migration were associated with a lower VZV seroprevalence [20]. VZV seroprevalence among female child day care workers (100%) also differed from seroprevalence among women not working in childcare (94%) [21]. Note that it was not possible to control for possible confounders such as age or ethnic background in this latter study.

A separate serosurveillance study conducted in 2016 among asylum-seekers in the Netherlands (18–45 years) showed that seroprevalence among people originating from Syria, Iran, Iraq, Afghanistan and Eritrea was high: 96% (range 92–98%) [22]. However, studies among asylum-seekers in Germany, Canada and Italy showed that seroprevalence varies considerably between countries of origin, and immunity depends on the age of the person concerned [23-25].

Preliminary results of the Health Study, part of the third PIENTER study conducted in Bonaire, Saint Eustatius and Saba in 2017, showed that the weighted overall VZV seroprevalence in the Caribbean Netherlands (78%) is considerably lower than in the Netherlands (95%) [26]. This is in line with the higher mean age of infection in tropical countries.

3.3 Varicella incidence in the Netherlands

The annual incidence of varicella in the Netherlands is based on general practitioner (GP) data. It is important to realise that not all patients with varicella consult a GP [27, 28], as varicella is usually seen as a mild disease everyone contracts during childhood. Combining GP data with VZV seroprevalence data shows that in the Netherlands only 1 in 4 people infected with VZV visit a GP because of varicella symptoms [3, 29].

The incidence of varicella per 100,000 population based on GP data differs by year (Table 3.1). According to a new, more precise method of estimating morbidity rates used by Nivel from 2012 onwards[*] [29, 30], the incidence of varicella (~260 GP episodes per 100,000 population) in the period 2012–2017 is somewhat higher than it was according to the old method (~245 GP episodes per 100,000 population), used in the period 2002–2011. Figure 3.2 shows that varicella is most common in children (<5 years). Another Dutch study found an incidence of varicella GP consultations of 515 per 100,000 (95%CI: 444–587) in the period 2004–2008 (377 per 100,000 when only ICPC codes were analysed) [31]. The incidence of acute cerebellar ataxia in the Netherlands is estimated at 5:100,000 VZV infections in children under 5 years of age [32]. The incidence of hospitalisations and deaths due to varicella is shown in Tables 3.2 and 3.3.

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[*] The method uses constructed episodes of illness (episodes are closed after 4 weeks without a reconsultation of the GP for varicella), based on an algorithm instead of the recorded 'raw' episodes of care used in the old method. This results in a more valid estimation of incidence rates, since the last moment in an episode of care is, in general, not the moment when the patient is considered to be cured. This new algorithm also results in higher incidence rates due to a smaller denominator, caused by more accurately estimated person years (due to better insights into the population 'at risk') [30].

Table 3.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72), based on the Nivel Primary Care Database (Nivel-PCD), using the old (2002–2011) and new method (2010–2017) (rounded to nearest ten)

GP consultation	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Incidence per 100,000*	320	270	250	190	300	210	(160)	(110)	(180)							
Incidence per 100,000**	190	160	200	130	260	230	290	180	210	230						
Incidence per 100,000***									310	270	250	280	270	250	240	280

* Dutch Sentinel General Practice Network (CMR) [33]; since 2008, this network has switched from registration on paper to electronic reporting, which may have resulted in under-reporting of the weekly number of varicella patients. We therefore used data from Nivel-PCD from 2008 onwards.
** Nivel-PCD, old method [34], *** Nivel-PCD, new method from 2012 onwards [29]; 2010–2011 recalculated.
Source: Nivel

Table 3.2 Absolute number and incidence per 100,000 population of hospitalisations (clinical admissions, excluding admissions for one day) due to main diagnosis of varicella (ICD-10 code B01), 2000–2014 [35]

Clinical admission	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Absolute number	211	233	219	273	269	238	313	231	271	242	315	277	253	281	321
Incidence per 100,000	1.3	1.5	1.4	1.7	1.7	1.5	1.9	1.4	1.7	1.5	1.9	1.7	1.5	1.7	1.9

Notes:
In 2006/2007, a number of hospitals ceased registration, causing an underestimation of hospital admissions from 2006 onwards.
The number of admissions may be higher than the number of hospitalised patients reported here because some patients are admitted more than once within the same year.
Hospitalisation data since 2015 are not yet available.
Source: DHD

Table 3.3 Absolute number and incidence per 100,000 population of deaths with varicella as primary cause of death (ICD-10 code B01), 2000–2018 [36]

Death	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018*
Absolute number	1	3	4	6	4	1	3	5	0	1	2	1	2	1	2	2	4	3	2
Incidence per 100,000	0.01	0.02	0.02	0.04	0.02	0.01	0.02	0.03	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.01

Source: CBS (*preliminary data)
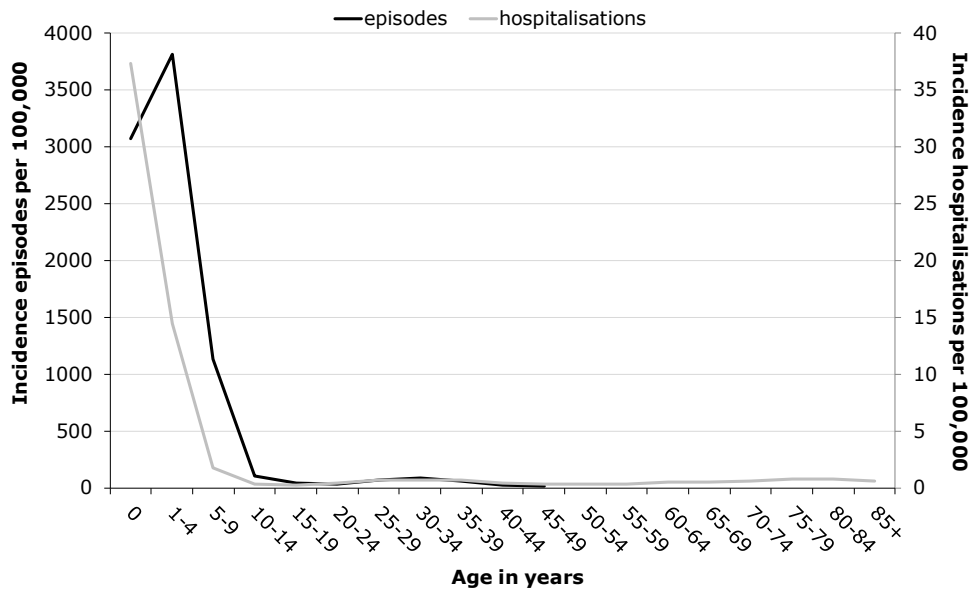
Figure 3.2 Estimated incidence per 100,000 population of episodes of varicella according to general practitioners in 2012–2017 and hospitalisations due to main diagnosis of varicella in 2000–2014, by age group [29, 35]

Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and are therefore not included.
Source: Nivel, DHD
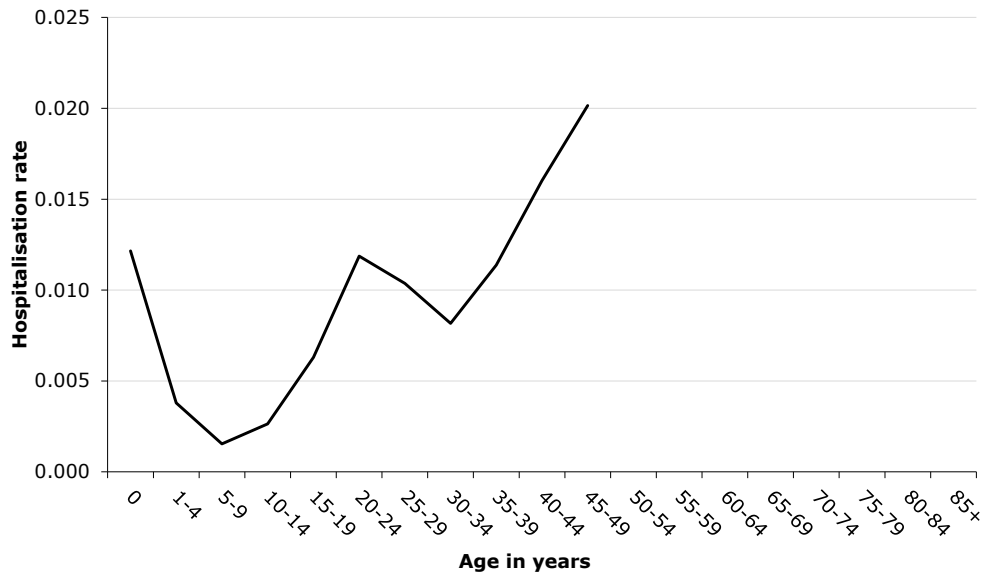
Figure 3.3 Mean hospitalisation rate (mean number of hospitalisations per 100,000 in 2000–2014 / mean number of GP consultations per 100,000 in 2012–2017 by age group [29]

Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and are therefore not included.
Source: Nivel/DHD

3.4   Morbidity and mortality due to varicella in the Netherlands

Based on the mean incidence in 2012–2017, a GP was visited for ~44,000 episodes of varicella annually (~40,000 in the period 2002–2011 based on the old method) (Table 3.1). In the period 2000–2014, ~260 patients were hospitalised with a main diagnosis of varicella annually (Table 3.2). There were 2.5 reported deaths with varicella as the main cause of death annually in the period 2000–2018 (range 0-6 deaths; 21% occurred in children <5 years of age) (Table 3.3). It is estimated that in the Netherlands, 1 in 4 people infected with VZV visit a GP because of varicella symptoms, 1 in 700 are hospitalised with main diagnosis varicella and 1 in 77,000 die with main cause of death varicella.

The hospitalisation rate can be defined as the number of hospitalised patients divided by the number of GP consultations. Figure 3.3 shows that the hospitalisation rate is relatively high among <1-year-olds and those in older age groups. This illustrates the higher risk on a severe course of varicella among very young children and adults.

It was hypothesised that varicella cases might be underreported in routine data of GP consultations (from Nivel) and hospitalisations (from DHD) in the Netherlands. Furthermore, due to the generally conservative consultation behaviour in the Netherlands, reported varicella cases might be more severe than in other countries. Therefore, the incidence of varicella GP consultations according to the routine Nivel data was compared with the incidence according to the Integrated Primary Care Information (IPCI) database. This database is a longitudinal GP research database, presently containing more than 1 million patient records from more than 400 GPs in the Netherlands; the patient population is representative of the Dutch population regarding sex and age [37]. The incidences based on these IPCI data were very similar to those based on the routine data of Nivel (Table 3.4). Varicella complications were registered in one-fifth (21%) of the 2,348 (probable) cases. The complications most often mentioned were bacterial superinfection of skin lesions (7% of all (probable) varicella cases), otitis media (5%), pharyngitis/tonsillitis (4%), conjunctivitis (2%) and gastroenteritis (1%); neurological complications were seen in 0.5%. Most of these complications were considered relatively mild and were treated by the GP; referral to secondary healthcare was limited (2%) [38].

Additionally, a study of the medical record of 296 hospitalised patients with a varicella diagnosis in the period 2003–2006 (32% <1 year of age, 49% 1–4 years of age, and 19% ≥5 years of age) was conducted to determine whether Dutch hospitalised cases due to varicella were more severe cases than in other countries. Complications were registered in 76% of the patients. The most frequently reported complications were bacterial superinfections of skin lesions (28%), (imminent) dehydration (19%), febrile convulsions (7%), pneumonia (7%) and gastroenteritis (7%). No varicella-related death occurred among the patients in this study but 3% had serious rest symptoms, such as residual ataxia/ coordination disorder (n=8; n=7 1–4 years of age/n=1 5–9 years of age) or cerebral nerve paralysis (n=2; n=1 5–9 years of age/n=1 55–59 years of age). This research showed that the severity of varicella-related

hospitalisations in the Netherlands was similar to that in other Western countries, despite the low incidence of hospitalisations generally in the Netherlands [39]. These additional studies confirmed that the disease burden due to varicella in the Netherlands is relatively low, which can probably be attributed to the young age of primary VZV infection [3, 40, 41].

It must be noted that the situation in the Caribbean Netherlands is different. Preliminary results of the Health Study (part of the third PIENTER study), performed in 2017 in this area, showed a lower VZV seroprevalence (see Section 3.2) highlighted by a varicella outbreak in Saba in 2017. The outbreak was considerable, with an estimated >250 varicella cases among a total population of 1,500 people on the island. Furthermore, based on information from GPs, large employers on the island and schools, it was estimated that one third of the cases were adults. This outbreak also caused varicella cases among pregnant women, some cases of varicella pneumonia and concerns about the occurrence of congenital varicella syndrome [42].

Table 3.4 Standardised incidence rates (IR) of general practitioner consultations and hospitalisations due to varicella per 100,000 by calendar year in IPCI compared with routine surveillance data (SENTINEL/LINH and LMR) [38]

	General practitioner consultations				Hospitalisations		
	IPCI min	IPCI max	SEN-TINEL	LINH	IPCI	LMR min	LMR max
Year	IR (95%CI)	IR (95%CI)	IR	IR	IR (95%CI)	IR	IR
2006	351 (318–388)	411 (375–451)	300	260	2.7 (0.9–8.4)	1.9	2.8
2007	268 (246–292)	320 (296–346)	210	230	1.9 (0.7–5.2)	1.4	2.1
2008	266 (250–284)	355 (336–376)	290		1.8 (0.9–3.8)	1.7	2.4
Overall	281 (268–294)	354 (340–369)	267[a]		2.0 (1.2–3.4)	1.7	2.4

IPCI = Integrated Primary Care Information; SENTINEL = Dutch sentinel general practice network; LINH = Dutch primary care database; LMR = National Medical Register.
IPCI min = minimum estimate based on the number of varicella cases; IPCI max = maximum estimate based on the sum of the number of varicella cases and cases with a probable diagnosis of varicella; LMR min = estimate based on the number of discharges with main diagnosis varicella; LMR max = estimate based on the number of discharges with main and/or side diagnosis varicella.

[a] For 2006 and 2007 SENTINEL data were used. Starting in 2008, the SENTINEL has changed from registration on paper to electronic reporting, which may have resulted in underreporting of the weekly number of varicella patients. Therefore, from 2008 onwards we used data for varicella surveillance based on ICPC codes in electronic medical records (EMRs) from LINH and sentinel general practices combined.

3.5   Burden of disease of varicella in the Netherlands

The burden of disease can be expressed in DALYs (disability-adjusted life years). This composite health measure combines morbidity (YLD=years lived with disability) and mortality (YLL=years of life lost) in a single measure. The total population burden of varicella (including herpes zoster) for all ages in 2017 was estimated at 1,800 (95% uncertainty interval (UI): 1,800–1,900) DALYs. This was lower than the burden of disease of most vaccine-preventable diseases in the year before the introduction of vaccination into the National Immunisation Programme (NIP) but higher than the burden of rotavirus gastroenteritis (1,100 (95%UI: 440–2,200) DALYs) and meningococcal B disease (620 (95%UI: 490–770) DALYs) (Figure 3.4). The burden of varicella alone was estimated at 160 DALYs, implying that most of the VZV burden (91%) was not caused by varicella but by herpes zoster [43].

CCa: cervical cancer (human papillomavirus (HPV)-16/18), Diph: diphtheria, HepB: hepatitis B, Hib: invasive *Haemophilus influenzae* type b disease, HZ: herpes zoster, Mea: measles, MenC/W/B: invasive meningococcal C/W/B disease, Mum: mumps, Pert: pertussis, Pneu: invasive pneumococcal disease (PCV10 types), Pol: poliomyelitis, Rota: rotavirus gastroenteritis, Rub: rubella, Tet: tetanus, Var: varicella.

Figure 3.4 Ranking of vaccine-preventable diseases by estimated disease burden (expressed in DALYs) at population and individual levels in the year before introduction of vaccination into the National Immunisation Programme or in 2017, the Netherlands, 1952–2017 [43]
DALY = disability-adjusted life years. Both axes are on a logarithmic scale. Black bubbles represent estimates for the year before inclusion in the National Immunisation Programme (NIP). White bubbles represent estimates for 2017 for potential NIP candidates. The area of each bubble is proportional to the average number of estimated cases (250 cases were added to each bubble for visibility reasons). The gradient colouring from the lower left quadrant to the upper right quadrant is used to indicate different levels of burden of disease (yellow: relatively low burden at population and individual level, i.e. mumps; red: relatively high burden at population and individual level, i.e. poliomyelitis); see full manuscript and Supplement 1 for all assumptions and limitations [43].

3.6   Varicella in other countries

3.6.1   *Seroepidemiology of VZV*

In temperate climates, varicella is a childhood disease. In tropical countries, the age of infection is considerably higher [7, 44]. This difference may be due to viral, host and geo-socio-climatic factors. For example, the dominant VZV genotype is not the same for every region, there are differences between rural and urban areas, and climatic factors are likely to influence VZV transmission [44].

Within the Asia-Pacific region, the increase in seropositivity with age in countries with a tropical or semi-tropical climate (e.g. Sri Lanka, Pakistan, Malaysia and Thailand) occurs at a slower rate than in countries with a more temperate climate, such as Australia and Taiwan [45]. Lee confirmed that several Asian countries (Singapore, Thailand, Malaysia, Philippines and India) exhibit a pattern typical of tropical countries [46]. The difference in seroprevalence between temperate and tropical or sub-tropical countries was also demonstrated by the review of Daulagala et al. [44]. In the Middle East, Africa, and Latin America and the Caribbean, data were limited and showed varying seroprevalence, mostly lower than in the Netherlands [47-49].

Seroprevalence data showed that in Europe almost everyone contracts VZV before adulthood [40, 41, 50, 51]. However, the age at which this happens varies; the highest seroprevalence was seen in the Netherlands (Figure 3.5). In a more recent analysis Bollaerts et al. distinguished three clusters on the basis of level of VZV seroprevalence: 1) ≥70% at the age of 5 (the Netherlands, Belgium and Luxembourg), 2) <70% at the age of 5, but ≥90% at the age of 10 age (Finland, France, Germany, Iceland, Ireland, Slovenia, Spain and Switzerland) and 3) <90% at the age of 10 (Greece, Italy, Poland, Slovakia and the United Kingdom) [41].
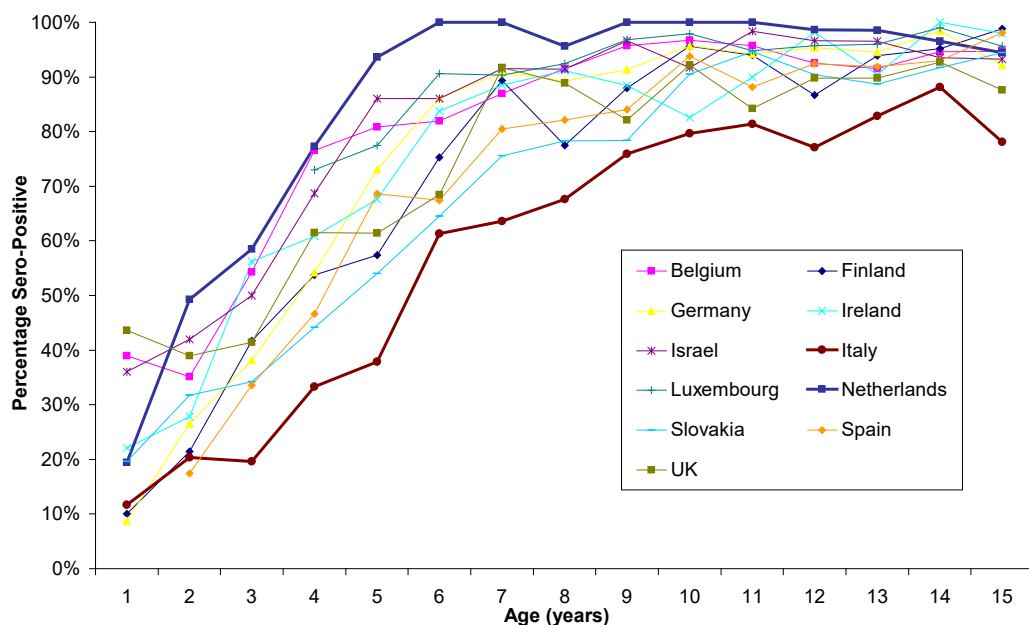

Figure 3.5 Age-specific standardised seroprevalence of VZV in 11 countries based on samples collected from residual sera or population sampling [40]

3.6.2 Morbidity and mortality due to varicella

Many reviews have been conducted on the epidemiology and/or burden of varicella in different regions of the world [41, 44, 46-55]. This section focuses on the situation in the Netherlands compared with other European countries and the United States.

In a previous analysis, the varicella-related morbidity and mortality figures for the Netherlands were compared with data from England and Wales because they have a comparable healthcare system, with access to primary healthcare through a GP. In England and Wales, there were 507 GP consultations in the period 2001–2007 [56], 5.8 hospital admissions (England only) in 2000/2001–2008/2009 [57], and 0.038 deaths in 2000–2008 [58] due to varicella per 100,000 population annually. These figures were more than twice as high as those for the Netherlands in the period 2000–2008 (238 GP consultations, 1.6 hospital admissions, and 0.018 deaths per 100,000 population) [39]. Note that updated figures for the Netherlands per 100,000 population showed comparable results: 260 GP episodes in the period 2012–2017, 1.6 hospitalisations in the period 2000–2014, and 0.015 deaths in the period 2000–2018 (see Section 3.3).

A more recent analysis by Riera-Montes et al. showed that the annual primary care incidence of varicella per 100,000 population was relatively low in the Netherlands compared with other European countries (before the introduction of universal childhood varicella vaccination). The same applies to the annual hospitalisation and mortality incidence of varicella per 100,000 population [55]. This was also illustrated by a review of Helmuth et al. [51].

In the United States, there were 4.2 (95%CI: 3.1–5.3) varicella-related hospitalisations per 100,000 population in the pre-vaccine era (1988-1995). This rate fluctuated by year from 3.3 in 1991 to 6.3 in 1995 [59]. During the period 1970–1994, there were 0.04 varicella-related deaths (primary cause) per 100,000 population [60]. These figures for the United States were also higher than those for the Netherlands (see above). It should be noted, however, that consultation behaviour is generally considered to be more conservative in the Netherlands than in other countries.

4   Vaccines against varicella

In 1974, researchers in Japan developed an attenuated strain of
varicella virus suitable for vaccine production, which they called the
OKA-strain [61, 62]. This strain is widely used in licensed vaccines
targeting varicella. Vaccination against varicella is available in two ways:
as a monovalent vaccine, containing only varicella vaccine virus, and as
part of a combination (multivalent) vaccine, containing measles,
mumps, rubella and varicella vaccine viruses (MMRV).

For all vaccines targeting varicella, a two-dose schedule is recommended
to increase the percentage of protected children and prevent
breakthrough infections (i.e. infection with wild-type VZV occurring in a
vaccinated person >42 days after varicella vaccination). In a 10-year
follow-up study of children receiving one or two doses of varicella-
containing vaccine, the risk of developing varicella >42 days post
vaccination during the 10-year observation period was 3.3 times lower
(P<0.001) in children who received two injections than in those who
received one injection (2.2% vs. 7.3%, respectively) [63]. A review of
severe breakthrough varicella cases showed that these were very rare
and always linked to a one-dose schedule [64].

Because all varicella-containing vaccines are live-attenuated, they are
contraindicated for: 1) immune-suppressed or immunocompromised
individuals, 2) people with active tuberculosis and 3) pregnant women.
Some products are also contraindicated during breastfeeding.
The European Medicines Agency undertook a review of the use of
monovalent and multivalent varicella vaccines during pregnancy and in
patients with weakened immune systems. They concluded that these
vaccines should be avoided during pregnancy, but that inadvertent
vaccination of pregnant women with MMR-containing vaccines should not
be a reason for termination of pregnancy. In addition, MMRV should not
be administered to patients with a severely weakened immune system,
but can be considered in cases of less severe immune deficiency [65, 66].
However, patients at high risk of severe varicella (patients with leukemia,
with a chronic disorder, or under immunosuppressive treatment, or those
for whom an organ transplant is planned) could benefit from vaccination
provided optimal timing of vaccination within the clinical setting.

In rare cases, vaccine virus can be transmitted from healthy vaccinated
individuals, whether or not they display a skin rash resembling varicella.
To prevent transmission, vaccinated individuals should avoid contact
with non-immune, vulnerable people, e.g. pregnant women, newborns
of mothers without documented varicella vaccination or infection and
immune-suppressed contacts. Furthermore, women should avoid
pregnancy for at least one month after vaccination.

In the Netherlands, one monovalent varicella vaccine (Provarivax®) and
two MMRV vaccines (ProQuad® and Priorix-Tetra®) are currently licensed
and available. The product-specific immunogenicity, efficacy and
effectiveness as well as the safety, of these vaccines is described below.
These data are mainly based on various studies as described in the

Summary of Product Characteristics (SmPC). Because the varicella vaccine strain of the monovalent vaccine Varilrix® is part of Priorix-Tetra®, which is licensed in the Netherlands, data on Varilrix® is also described, although this vaccine is currently not available for use in the Netherlands. Regarding post-marketing data on immunogenicity, effectiveness, and safety, it is often difficult to assign the information to a specific product. As companies are obliged to report all notifications, irrespective of causality, reported adverse events (AEs) do not necessarily reflect the 'true' safety profile.

4.1 Provarivax®

Provarivax® (called Varivax® in other countries) is a monovalent varicella vaccine, indicated for infants and adults aged 12 months or older. The two doses have different, age-dependent, intervals [67]. This vaccine is also a component of the combination vaccine ProQuad® (MMRV).

4.1.1 *Immunogenicity*
Infants and children
Seroconversion, based upon a ≥0.6 gpELISA units cut-off, was observed in 98% of 9,610 susceptible children aged 12 months to 12 years following one dose with 1,000 to 50,000 plaque-forming units (PFU). In about 83% of these children, anti-varicella antibody concentrations ≥5 gpELISA units were found. This is highly indicative of long-term protection [67].

Follow-up of a subset of this cohort showed that the percentage of children with detectable antibodies remained stable over a six-year period. During nine years of follow-up of children receiving one dose or two doses, the level of geometric mean titers (GMTs) and the percentage of seroconverted children were higher in the two-dose group than in the one-dose group during the first year. Thereafter, they were comparable, with respectively 99.0% and 98.8% seroconversion in the ninth year of follow-up [67].

Adolescents and adults
In several clinical trials including 934 people aged 13 years and more, 73–100% seroconverted (≥0.6 gpELISA units anti-varicella antibody concentrations) following a single dose with 900–17,000 PFU. In 22–80%, antibody concentrations were ≥5 gpELISA units. After two doses (601 people), 97–100% seroconverted, with 76–98% having antibody concentrations ≥5 gpELISA units [67].

Follow-up studies of twice-vaccinated people aged 13 years and older showed that ≥97% had detectable antibody concentrations up to six years after vaccination. It is likely that the long-term detectable antibody concentration found during follow-up is due to contact with circulating wild-type virus [67].

4.1.2 *Vaccine efficacy and effectiveness*
Infants and children
In combined clinical studies with previous formulations of the vaccine at doses ranging from 1,000 to 17,000 PFU, the majority of subjects

(healthy children between 12 months and 12 years of age) who received one dose of the varicella vaccine and were exposed to the natural virus were either fully protected against varicella or experienced a mild form of the disease.

In particular, the protective effect of one dose of the varicella vaccine from 42 days after vaccination onwards was evaluated in three different ways:

1. in a double-blind, placebo-controlled study for 2 years (n=956; efficacy 95–100%; formulation with 17,430 PFU);
2. by evaluating the protection against disease after home exposure for 7 to 9 years of observation (n=259; efficacy 81–88%; formulation with 1,000–9,000 PFU); and
3. by comparing the varicella incidence for 7 to 9 years in vaccinees with historical control data from 1972 up to and including 1978 (n=5,404; efficacy 83–94%; formulation with 1,000–9,000 PFU) [67].

In a group of 9,202 children aged 12 months to 12 years who had received one dose of the varicella vaccine, 1,149 were reported as experiencing an infection (occurring more than 6 weeks after vaccination) over a follow-up period of up to 13 years. Of these 1,149 cases, 20 (1.7%) were classified as severe (number of lesions ≥300, oral body temperature ≥37.8°C). This corresponds to a relative reduction of 95% in the number of serious cases in vaccinated individuals [67].

In a comparative study of one dose (n=1,114) with two doses (n=1,102) of the varicella vaccine administered to healthy children aged 12 months to 12 years at a 3-month interval, the evaluated efficacy against all grades of varicella severity over the 10-year observation period was 94% for one dose and 98% for two doses (p<0.001). During this 10-year observation period, the cumulative percentage of varicella cases was 7.3% after one dose and 2.2% after two doses. The majority of the reported cases of varicella in vaccinated individuals with one or two doses were mild [63, 67].

Besides the above results of clinical trials, results of observational studies confirmed the efficacy of varicella vaccination at about 90%. In a prospective long-term cohort study, about 7,600 children who were vaccinated with varicella vaccine in their second year of life in 1995 were actively followed for 14 years to estimate the incidence of varicella and herpes zoster. At the end of the study in 2009, 38% of the children studied had received a second dose. During the full follow-up, the incidence of varicella was about 10 times lower among vaccinees than among children of the same age in the pre-vaccination period. The estimated vaccine efficacy during the study period was between 73% and 90%. The risk on herpes zoster was also lower among vaccinees (relative risk 0.61 (95%CI: 0.43–0.89). Breakthrough cases of varicella and herpes zoster were usually mild [67].

In another long-term surveillance study, five cross-sectional measurements of varicella incidence were performed within a period of 15 years, each in a random sample of about 8,000 children and adolescents aged 5 to 19 years, from 1995 (pre-vaccination) to 2009.

Results showed a gradual decrease in varicella frequencies of 90% to 95% in total from 1995 to 2009 in all age groups; this applied to both vaccinated and unvaccinated children. In addition, a decrease in varicella hospitalisations of about 90% was observed in all age groups [67].

Adolescents and adults
The protective effect after two doses of varicella vaccine, administered at intervals of 4 or 8 weeks, to persons 13 years and older was evaluated on the basis of home exposure for 6 to 7 years after vaccination. The clinical efficacy varied from approximately 80% to 100% [67].

4.1.3   *Safety*
Infants and children
A double-blind randomised controlled trial in healthy individuals aged 12 months to 14 years (n=956) reported comparable frequencies of adverse events (AEs) in the vaccinated group and the placebo group. Only pain (26.7% vs 18.1%) and redness (5.7% vs 2.4%) at the injection site and a varicella-like skin rash (2.2% vs 0.2%) were significantly more often reported in the varicella vaccine group [67]. In clinical studies with causality assessment of AEs (5,185 children aged 12 months to 12 years), diarrhoea, fever convulsion, fever, post-infectious arthritis and vomiting were reported as serious adverse events (SAEs) and in time associated with the varicella vaccination. Systemic AEs were equally distributed between the two doses or more often reported after the first dose, while injection site reactions more often occurred after the second dose [67].

In clinical studies, 12 cases of herpes zoster were reported during follow-up in 9,543 vaccinated people aged 12 months to 12 years, resulting in an incidence of 14 per 100,000 compared with 77 per 100,000 following wild-type infection. Cases showed a mild disease course without complications [67].

Adolescents and adults
In clinical studies in people aged 13 years and over (n=1,648) varicella-like skin rash, fever, injection site rash and itch were reported as SAEs in time associated with the vaccination [67].

In 1,652 vaccinated people aged 13 years and over, two cases of herpes zoster were reported. Cases showed a mild disease course without complications [67].

4.2   Varilrix®

Varilrix® is a monovalent varicella vaccine, indicated for infants and adults aged nine months or older. Some countries recommend the vaccine from 12 months onwards. The two doses have different, age-dependent, intervals [68, 69]. To date, this vaccine is not licensed in the Netherlands, though it is also a component of the licensed combination vaccine Priorix-Tetra® (MMRV) (see Section 4.4).

4.2.1   *Immunogenicity*
Infants and children
In children aged 11 to 21 months, the seroconversion rate measured with ELISA, Enzygnost, Dade Behring (50 mIU/ml) 6 weeks after administration of a dose of vaccine reached 89.6%; after administration of a second dose of vaccine it reached 100%.
In children from 9 months to 12 years of age inclusive, the seroconversion rate measured by immunofluorescence 6 weeks after administration of a dose of vaccine exceeded 98%. In children from 12 to 15 months of age, antibodies persisted for at least 7 years after vaccination with a single dose.
In children from 9 months to 6 years of age, the seroconversion rate measured by immunofluorescence six weeks after administration of a second dose of vaccine was 100%. An appreciable increase in antibody titers was observed after administration of a second dose (the GMT increased by a factor of 5 to 26) [68, 69].

Adolescents and adults
In subjects 13 years of age and over, the seroconversion rate measured by immunofluorescence six weeks after administration of a second dose of vaccine was 100%. One year after vaccination, all the subjects tested were still seropositive [68, 69].

4.2.2   *Vaccine efficacy and effectiveness*
The efficacy of Varilrix® (and Priorix-Tetra®) was measured in a large randomised clinical trial with the MMR vaccine Priorix® as control. In this trial, 2,263 children aged 12–22 months received one dose of Priorix® and after 6 weeks one dose of Varilrix® and were followed up for approximately 35 months post vaccination. The observed vaccine efficacy of one dose of Varilrix® against epidemiologically confirmed or PCR confirmed varicella of any severity was 65.4% (97.5%CI: 57.2–72.1%), and against moderate or severe confirmed varicella 90.7% (97.5%CI: 85.9–93.9%) [68, 70]. After 6 years, the efficacy against all and against moderate or severe varicella was 67.0% (95%CI: 61.8–71.4%) and 90.3% (95%CI: 86.9–92.8%), respectively [71]. After 10 years, the efficacy against all and against moderate or severe varicella was 67.2% (95%CI: 62.3–71.5%) and 89.5% (95%CI: 86.1–92.1%), respectively [72].

In a study in Finland, 493 children aged 10–30 months were followed up for approximately 2.5 years after vaccination with one dose of Varilrix®. The efficacy against common or severe clinical varicella (≥30 vesicles) was 100% (95%CI: 80–100%) and against any serologically confirmed varicella (at least 1 vesicle or papule) was 88% (95%CI: 72–96%) [68, 73].

The effectiveness of one dose of Varilrix® estimated in different settings (outbreaks, case-control and database studies) ranged from 20%–92% against any varicella, and from 86%–100% against moderate or severe varicella [68].

4.2.3 *Safety*
Infants and children
In a clinical trial, 272 children aged 12 to 24 months were randomised in four groups, i.e. three groups receiving MMR of different manufacturers and one group receiving MMR (Priorix®) + Varilrix®. Rates of fever were 59% ≥38.1°C and 19.7% ≥39.5°C in the MMR+V group. In one MMR group these rates were 61.3% ≥38.1°C and 17.7% ≥39.5°C; in the other two MMR vaccine groups the rates were lower. Rash was observed in all groups, with the highest rates of 7.1% in the third MMR group and 4.9% in the MMR+V group. Local symptoms were minimal in the MMR+V group: pain in 3.3% and 3.3%, redness in 6% and 3.3% and swelling in 0% and 3.3% in the Varilrix and MMR groups, respectively [69].

Infants, children, adolescents and adults
Based on a total of 5,369 single doses of the vaccine to children, adolescents and adults, pain and redness at the injection site were reported in ≥1/10 vaccinees. Swelling at the injection site, fever ≥37.5°C and <39°C and eruptions had a frequency of ≥1/100–<1/10, while upper respiratory tract infections, pharyngitis, cough, rhinitis, lymphadenopathy, irritability, headache, drowsiness, nausea, vomiting papulo-vesicular eruptions, pruritus, arthralgia, myalgia, fever ≥39.0°C, fatigue and malaise were uncommonly reported, i.e. ≥1/1,000–<1/100. Conditions that are reported rarely (≥1/10,000–<1/1,000) were conjunctivitis, abdominal pain, diarrhoea and urticaria.
Injection site reactions were reported more often after a second dose than after the first dose. No difference was noted in the reactogenicity profile between initially seropositive and initially seronegative subjects [68].

4.3 **ProQuad®**
ProQuad® is a combination vaccine, containing measles, mumps, rubella and varicella vaccine viruses. The vaccine is indicated for infants and adults aged 12 months or older. The interval between two doses should be at least 4 weeks [74].

4.3.1 *Immunogenicity*
Infants and children
A single dose of ProQuad® was highly immunogenic in initially seronegative 12–23-month-olds. Six weeks after vaccination, response rates were 97.4% for measles, 98.8% for mumps, 98.5% for rubella and 91.2% for varicella (≥5 gpELISA units/ml). In seroconverted individuals, antibody persistence rates one year after vaccination with ProQuad® were 98.9% (measles), 96.7% (mumps), 99.6% (rubella) and 97.5% (varicella).
In a two-dose regimen (n=1,035) with a 3-month interval, response rates 6 weeks after the second dose remained above 98% for measles, mumps and rubella, with a 1.7–2.4-fold increase of GMTs. VZV responses increased from 86.6% after one dose to 99.4% after two doses, with a ~41-fold increase in GMTs.
Likewise, a two-dose schedule with a second dose at 4 to 6 years of age (n=399) resulted in seropositivity rates of ≥98.8% for all four vaccine

components, with 1.2, 2.4, 3.0 and 12.4 GMT rises for measles, mumps, rubella and VZV, respectively [75].

4.3.2 *Vaccine efficacy and effectiveness*

Formal studies to evaluate the efficacy of ProQuad® have not been conducted. However, the efficacy of its separate components MMR and Provarivax® has been demonstrated in several studies (see Section 4.1). The efficacy of ProQuad® was established through the use of immunological correlates for protection against measles, mumps, rubella and varicella. Clinical studies with a single dose of ProQuad® showed that vaccination elicited similar antibody responses for varicella as a single dose of Provarivax® [74].

4.3.3 *Safety*

Infants and children

Clinical registration trials with 4,424 children receiving ProQuad® (cases) and 1,997 children receiving MMR®II and Varivax® (controls) showed that 47.6% and 50.4% of cases and controls, respectively, reported one or more AEs. In the two groups, local reactions were reported in 31.3% and 34.4%, while systemic AEs were seen in 33.0% and 28.1%, respectively. The higher frequency of systemic AEs in cases was merely related to statistically significant higher frequencies of fever (21.5% vs 14.9%) and measles-like rash (3.0% vs 2.1%). The fever episodes in cases had an average duration of 1.7 days, with 61% of fever rated as mild by the subject's parent. Fever ≥40°C within 5–12 days of vaccination occurred in 2.9% and 2.0% of cases and controls, respectively (p=0.041). Varicella-like rash was reported in comparable frequencies in both groups, i.e. 2.1% and 2.2% among cases and controls, respectively. The numbers of febrile seizures in this time window were comparable (0.14% vs 0.25%). However, studies did not have enough power to detect significant differences in rare AEs. Reports of fever and measles-like rash were associated with higher GMTs to measles, and older age was a predictor of fever. The level of VZV potency in cases was not associated with a change in the rate of measles-like rashes; nor was it a predictor of fever.

In cases who received a second dose of ProQuad®, frequencies of local and systemic AEs were lower than after a first dose [75].

4.4 Priorix-Tetra®

Priorix-Tetra® is a combination vaccine, containing measles, mumps, rubella and varicella vaccine viruses. The vaccine is indicated for infants and children aged 11 months to 12 years. In a special epidemiological situation, a first dose can be given from the age of 9 months. The interval between two doses should be 6 to 12 weeks, with specific and smaller intervals in younger children [76].

4.4.1 *Immunogenicity*

Infants and children

Seroconversion rates after a first dose of MMRV (cases) and MMR+V (controls) were measured. In both groups, these were lowest for mumps (91.3% and 93.9%, respectively) and highest for rubella (99.7% and 99.2%, respectively). After the second dose, seroconversion rates were

>98.0% for all components in both groups, with 1.7–1.8-fold higher GMTs after the second dose compared with the first dose.
The measles seropositivity rate decreased slightly at 3 years post-immunisation to 99.0% in the MMRV group and 97.0% in the MMR+V group. For mumps, these percentages were 97.4% and 93.8%, respectively. Rubella seropositivity remained at 100% in both groups, while varicella seropositivity was 99.4% in the MMRV group and 96.8% in the MMR+V group after three years of follow-up. The number of varicella breakthrough infections was slightly lower in the MMRV group (n=2) compared with the MMR+V group (n=5) [77].

4.4.2   *Vaccine efficacy and effectiveness*
The efficacy of Priorix-Tetra® (and Varilrix®) was measured in a large randomised clinical trial with the MMR vaccine Priorix® as control. In this trial, 2,279 children aged 12–22 months received two doses of Priorix-Tetra® six weeks apart and were followed up for approximately 35 months post vaccination. The observed vaccine efficacy against epidemiologically confirmed or PCR-confirmed varicella of any severity was 94.9% (97.5%CI: 92.4–96.6%) and against moderate or severe confirmed varicella 99.5% (97.5%CI: 97.5–99.9%) [70, 76]. After 6 years, the efficacy against all varicella and against moderate or severe varicella was 95.0% (95%CI: 93.6–96.2%) and 99.0% (95%CI: 97.7–99.6%), respectively [71]. After 10 years, the efficacy against all and against moderate or severe varicella was 95.4% (95%CI: 94.0–96.4%) and 99.1% (95%CI: 97.9–99.6%), respectively [72].

4.4.3   *Safety*
Infants and children
With respect to solicited local symptoms within four days of a first dose, no significant differences were observed between the MMRV group (n=2,206; cases) and the MMR+V group (n=574; controls). Participants were 12 to 20 months old. Frequencies of pain were 9.47% (95%CI: 8.28–10.77%) in cases and 8.71% (95%CI: 6.53–11.32%) in controls. For redness, these percentages were 27.02% vs 27.35%; for swelling 8.43% and 8.01%. After a second dose of MMRV, frequencies of local reactions were slightly higher than following the first dose. For a second dose of MMR (without concomitant V), frequencies of local reactions were lower than after the first MMR+V. Grade 3 (i.e. severe) local reactions were <1% in both groups after both doses, except for grade 3 redness after a second dose of MMRV (3.36%; 95%CI: 2.64–4.21%). No statistically significant differences were found between the two groups in the occurrence of measles, rubella or varicella-like rash observed after either dose. Rashes occurred less frequently following a second dose of MMRV or MMR+V.
For systemic AEs, fever during the first 15 days after the first dose more frequently occurred following MMRV (61.15%; 95%CI: 59.08–63.19%) compared with MMR+V (45.82%; 95%CI: 41.69–49.99%; p<0.05). Fever ≥39.5ºC occurred in 11.20% and 7.49% in the MMRV and MMR+V groups, respectively (p<0.05). After the second dose, the incidence of fever was lower than after the first dose in both groups, and no differences were observed between the groups [77].

4.5 Post-marketing immunogenicity of mono- and multivalent varicella vaccines

A systematic review of the immunogenicity and safety of MMRV vaccines in healthy children, including 19 randomised controlled trials (RCTs), showed that seroconversion rates of the MMRV viruses were similar across the groups compared, i.e. MMRV vs MMR with or without V. There were comparable GMTs against mumps and varicella viruses between the MMRV group and the MMR + V/MMR group. The MMRV group achieved an enhanced immune response to the measles component, with a GMT ratio of 1.66 (95%CI: 1.48–1.86; P<0.001) for MMRV versus MMR and 1.62 (95%CI: 1.51–1.70; P<0.001) for MMRV versus MMR + V. On the other hand, the immune response to the rubella component in MMRV group was slightly reduced; GMT ratios were 0.81 (95%CI: 0.78–0.85; P<0.001) and 0.79 (95%CI: 0.76–0.83; P<0.001), respectively [78].

The clinical trial including Dutch participants (included in the review described above) and studying the optimal interval between consecutive doses of MMRV (Priorix-Tetra®) in 11–13-month-old children found a 71.3% seroconversion rate for mumps 4 weeks after dose 1 in the MMRV-4-weeks group. Seroconversion for the other components ranged from 97.2% to 98.9%, and the MMR group showed similar seroconversion rates for mumps, measles and rubella. Six weeks after dose 1 in the MMRV-12-months group, seroconversion rates for all components were high (94.0–98.4%), and antibodies persisted to give similarly high seroconversion rates 1 year after the first dose. Seroconversion rates for each vaccine component were within the same range in all treatment groups 6 weeks after the second dose. However, GMTs for all vaccine components tended to be higher 6 weeks after the second dose when administered at month 12 versus at week 4. Likewise, the GMTs in the MMRV-12-months group tended to be higher than in the MMR group. Antibody persistence one year after dose 2 was similar in the MMRV-4-weeks and the MMR groups, with seroconversion rates ranging from 98% to 100% for measles and rubella, and from 91.1% to 92.1% for mumps. Two cases of varicella breakthrough infections were reported in the MMRV-12-months group [79].

A randomised, double-blind clinical study, with three groups - two groups receiving different dosages of Varivax® + MMR (n=206 and n=205) and one group receiving Varilrix® + MMR (n=203) - also assessed immunogenicity in these three groups. Results show that both dosages of Varivax® + MMR had higher GMTs and a higher frequency of children with a 6-week post-vaccination concentration ≥5gpELISA compared with the group receiving Varilrix® + MMR (see Table 4.1) [80].

Table 4.1 GMTs and percentage of children with a ≥5gpELISA anti-varicella antibody concentration 6 weeks post vaccination [80]

	High dose Varivax® + MMR	Low dose Varivax® + MMR	Varilrix® + MMR
GMT (95%CI)	14.2 (12.6–15.9)	16.7 (14.9–18.6)	9.4 (8.4–10.4)
≥5gpELISA anti-varicella antibody concentration (95%CI)	96.8% (93.2–98.8%)	95.3% (91.2–97.8%)	85.6% (79.8–90.2%)

4.6 Post-marketing vaccine effectiveness of mono- and multivalent varicella vaccines

Vaccine effectiveness concerns the effect of vaccines in real-world settings. Varicella vaccine effectiveness has been assessed in outbreak, case-control and longitudinal, database, observational, and modelling studies. Note that in most of the studies, vaccine effectiveness was assessed during outbreak investigations using clinically diagnosed varicella.

Based on a systematic review and descriptive and meta-analysis of the Medline, Embase and Cochrane libraries and CINAHL databases of reports published during 1995–2014, Marin et al. estimated post-licensure varicella vaccine effectiveness among healthy children. The pooled 1-dose vaccine effectiveness of monovalent varicella vaccines was 81% (95%CI: 78–84%) against all varicella and 98% (95%CI: 97-99%) against moderate/severe varicella; there was no difference by vaccine type or study design (see Figures 4.1 and 4.2). The pooled 2-dose vaccine effectiveness of monovalent varicella vaccines against all varicella was 92% (95%CI: 88–95%); there was no difference by study design (see Figure 4.3). The only vaccine effectiveness reported for MMRV/Priorix-Tetra© was against all varicella: 55% (95%CI: 8–78%) for 1 dose and 91% (95%CI: 65–98%) for 2 doses [81].

Yin et al. conducted a systematic literature review and meta-analysis to estimate the incremental vaccine efficacy/effectiveness of 2-dose versus 1-dose varicella vaccination among healthy children. The incremental vaccine efficacy/effectiveness of 2-dose vaccination was estimated at 79% (95%CI: 56−90%) in randomised controlled trials, 63% (95%CI: 36−79%) in cohort studies and 81% (95%CI: 65−90%) in case-control studies (see Figure 4.4) [82].

In a non-systematic review, Varela et al. addressed the impact of universal varicella vaccination in the Americas, Europe, Africa, Oceania and Asia. In most studies with a longer follow-up, the reduction in varicella incidence and hospitalisations was greater than 80%. The additional effect of a second dose and indirect protection in non-vaccinated groups has also been confirmed in multiple studies [83].

A literature review by Wutzler et al., summarising the effectiveness and epidemiological impact of varicella immunisation programmes, showed high effectiveness of varicella vaccines against varicella – particularly moderate or severe varicella. Effectiveness against all varicella ranged from 55% to 87% after one dose and from 84% to 98% after two

doses. For moderate or severe varicella, the effectiveness ranged from 70% to 98% after one dose and from 94% to 98% after two doses [84].

Helmuth et al. performed a review of epidemiological studies conducted in Europe from 2004 to 2014. In countries that had introduced varicella vaccination (Germany, Italy and Spain) this had resulted in a rapid decrease in varicella incidence and hospitalisations, with herd protection effects in unvaccinated groups, such as children <1 year of age [51].

Seward et al. reviewed the published results of post-licensure studies of varicella vaccine effectiveness over the period 1995–2006, for varicella vaccines licensed in the United States (Varivax© and ProQuad©). Overall, the effectiveness of one dose of monovalent varicella vaccine was 44-100% (mean, 80.7%; median, 84.5%) against all varicella, 86-100% (mean, 96.1%; median, 97.0%) against combined moderate and severe varicella, and 100% (mean and median) against severe varicella. Most studies found a somewhat lower vaccine effectiveness against all varicella than described in the initial RCT (98% after 2 years of follow-up). There were no published post-licensure studies of the effectiveness of the MMRV vaccine [85].

Quinn et al. showed moderate protection of a 1-dose varicella vaccination programme (mainly Varilrix©) in Australia: the estimated case-control vaccine effectiveness against hospitalised varicella was 64.2% (95%CI: 41.7–78.1%) [86].

Varicella vaccine effectiveness against varicella of any severity showed no waning for up to 14 years [87].
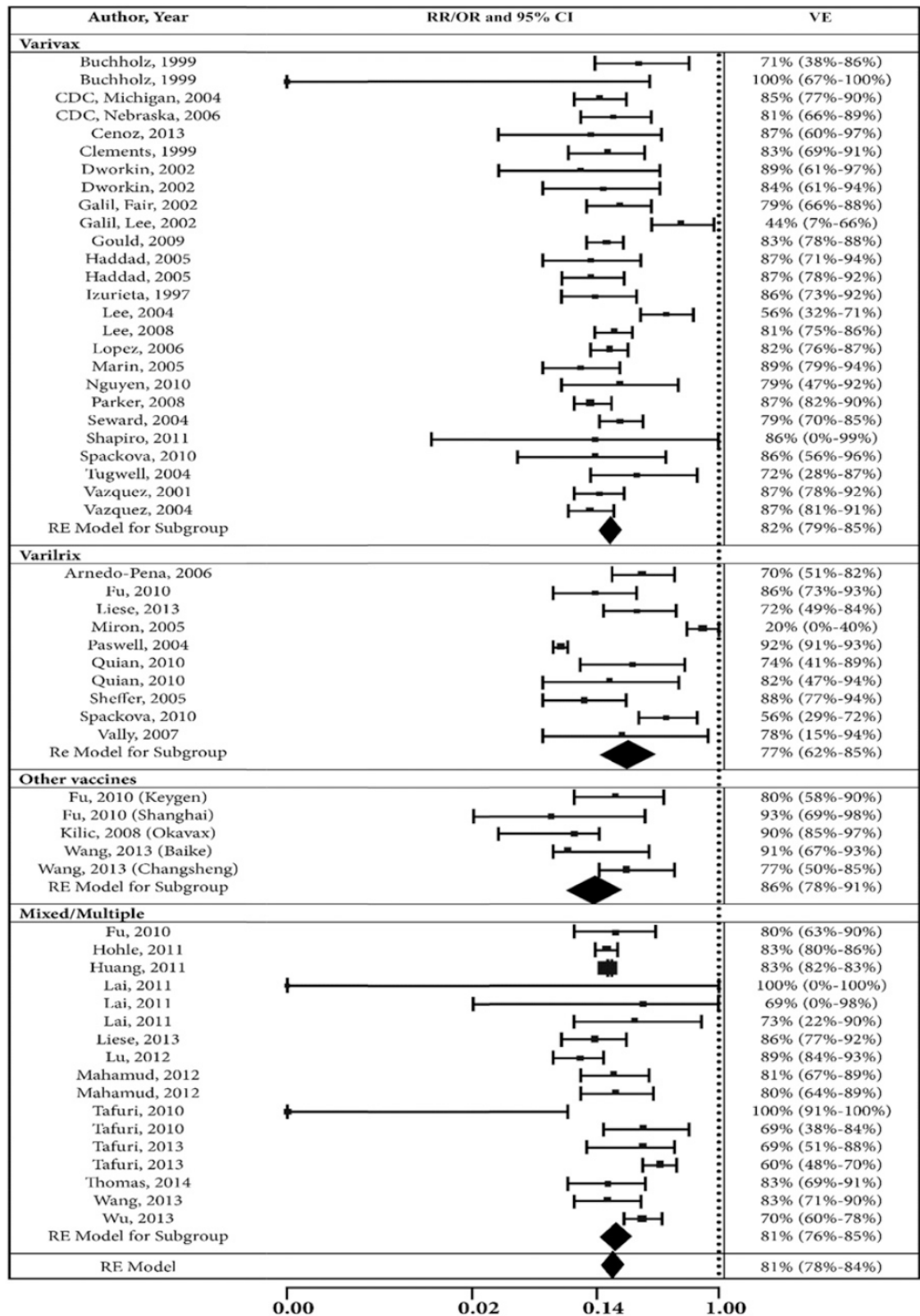
Author, Year	RR/OR and 95% CI	VE
Varivax		
Buchholz, 1999		71% (38%-86%)
Buchholz, 1999		100% (67%-100%)
CDC, Michigan, 2004		85% (77%-90%)
CDC, Nebraska, 2006		81% (66%-89%)
Cenoz, 2013		87% (60%-97%)
Clements, 1999		83% (69%-91%)
Dworkin, 2002		89% (61%-97%)
Dworkin, 2002		84% (61%-94%)
Galil, Fair, 2002		79% (66%-88%)
Galil, Lee, 2002		44% (7%-66%)
Gould, 2009		83% (78%-88%)
Haddad, 2005		87% (71%-94%)
Haddad, 2005		87% (78%-92%)
Izurieta, 1997		86% (73%-92%)
Lee, 2004		56% (32%-71%)
Lee, 2008		81% (75%-86%)
Lopez, 2006		82% (76%-87%)
Marin, 2005		89% (79%-94%)
Nguyen, 2010		79% (47%-92%)
Parker, 2008		87% (82%-90%)
Seward, 2004		79% (70%-85%)
Shapiro, 2011		86% (0%-99%)
Spackova, 2010		86% (56%-96%)
Tugwell, 2004		72% (28%-87%)
Vazquez, 2001		87% (78%-92%)
Vazquez, 2004		87% (81%-91%)
RE Model for Subgroup		82% (79%-85%)
Varilrix		
Arnedo-Pena, 2006		70% (51%-82%)
Fu, 2010		86% (73%-93%)
Liese, 2013		72% (49%-84%)
Miron, 2005		20% (0%-40%)
Paswell, 2004		92% (91%-93%)
Quian, 2010		74% (41%-89%)
Quian, 2010		82% (47%-94%)
Sheffer, 2005		88% (77%-94%)
Spackova, 2010		56% (29%-72%)
Vally, 2007		78% (15%-94%)
Re Model for Subgroup		77% (62%-85%)
Other vaccines		
Fu, 2010 (Keygen)		80% (58%-90%)
Fu, 2010 (Shanghai)		93% (69%-98%)
Kilic, 2008 (Okavax)		90% (85%-97%)
Wang, 2013 (Baike)		91% (67%-93%)
Wang, 2013 (Changsheng)		77% (50%-85%)
RE Model for Subgroup		86% (78%-91%)
Mixed/Multiple		
Fu, 2010		80% (63%-90%)
Hohle, 2011		83% (80%-86%)
Huang, 2011		83% (82%-83%)
Lai, 2011		100% (0%-100%)
Lai, 2011		69% (0%-98%)
Lai, 2011		73% (22%-90%)
Liese, 2013		86% (77%-92%)
Lu, 2012		89% (84%-93%)
Mahamud, 2012		81% (67%-89%)
Mahamud, 2012		80% (64%-89%)
Tafuri, 2010		100% (91%-100%)
Tafuri, 2010		69% (38%-84%)
Tafuri, 2013		69% (51%-88%)
Tafuri, 2013		60% (48%-70%)
Thomas, 2014		83% (69%-91%)
Wang, 2013		83% (71%-90%)
Wu, 2013		70% (60%-78%)
RE Model for Subgroup		81% (76%-85%)
RE Model		81% (78%-84%)

0.00   0.02   0.14   1.00

Figure 4.1 Random effects model of 1-dose varicella vaccine effectiveness for prevention of all varicella, by vaccine [81]
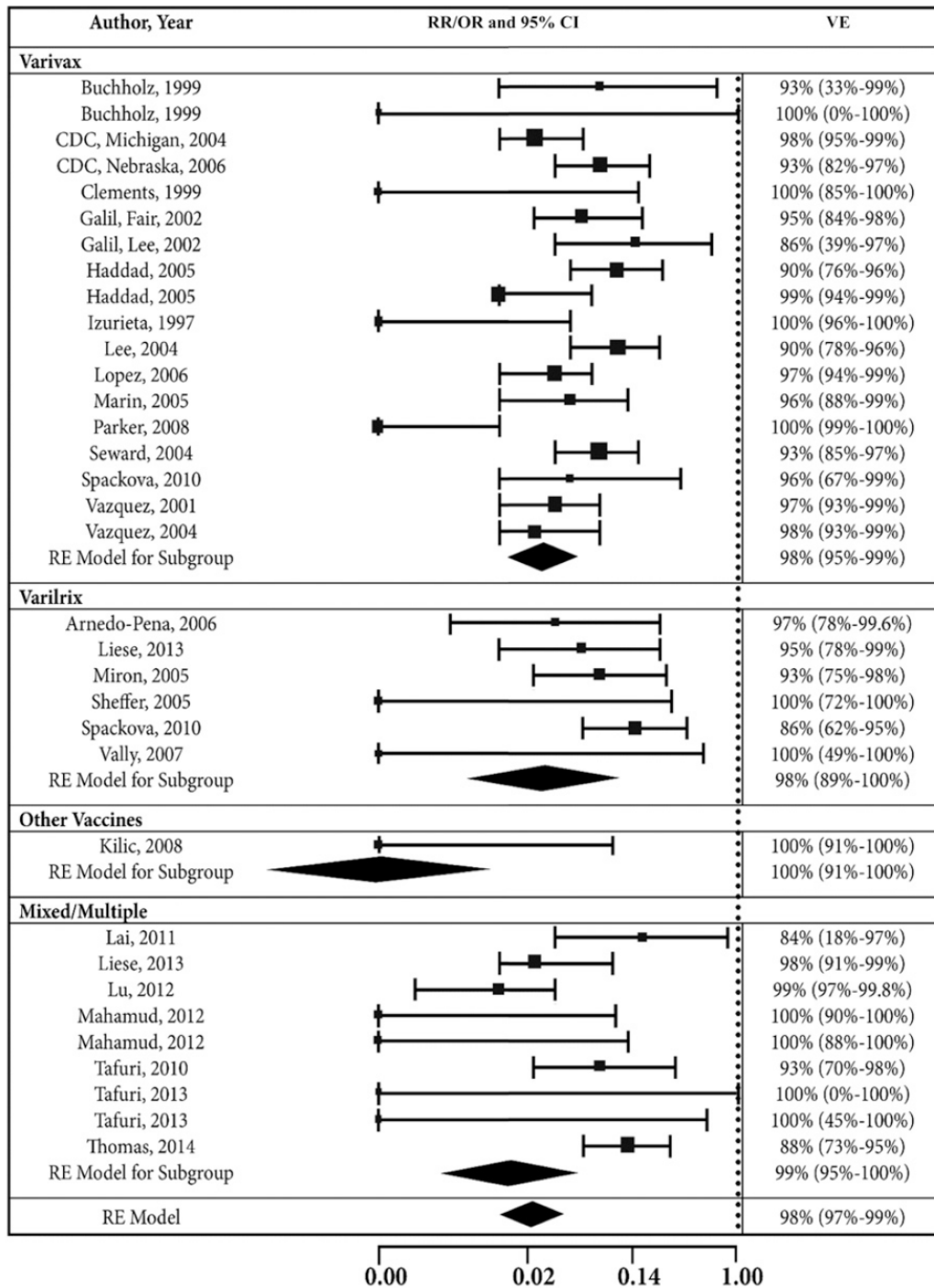
Figure 4.2 Random effects model of 1-dose varicella vaccine effectiveness for prevention of combined moderate and severe varicella, by vaccine [81]
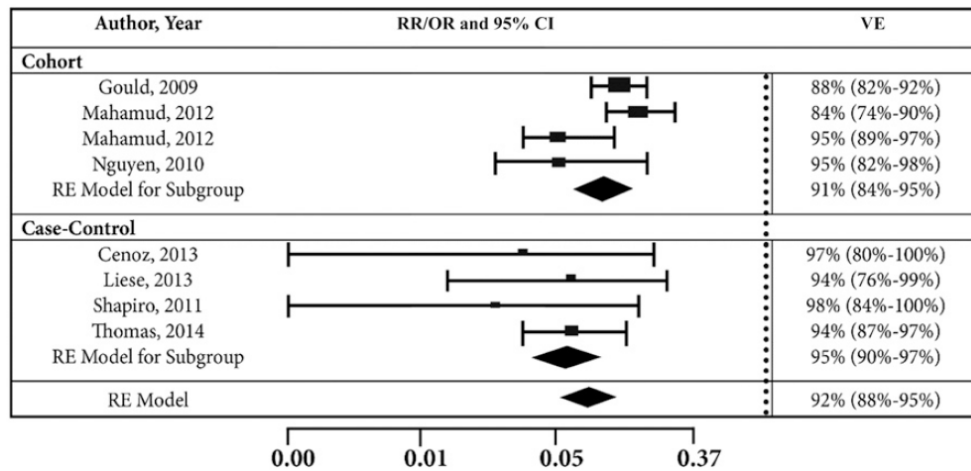
Figure 4.3 Random effects model of 2-dose varicella vaccine effectiveness for prevention of all varicella, by study design [81]

4.7 Post-marketing safety of mono- and multivalent varicella vaccines

Surveillance of spontaneous reported AEs through the Vaccine Adverse Events Reporting System (VAERS) of the United States for 1995–2005 showed a reporting incidence of 52.7/100,000 AEs following varicella vaccination. The most commonly reported AE was rash (17.3/100,000 doses), accounting for 32.6% of all reports; 64.0% of these were related to varicella vaccine administered alone. Fever (11.4/100,000 doses) and injection-site reactions (6.9/100,000 doses) accounted for 21.5% and 13.0% of reports, respectively. Serious AEs were reported rarely [88].

A systematic review of the immunogenicity and safety of MMRV vaccines in healthy children, including 19 RCTs, showed that these vaccines are well tolerated. However, compared with MMR without V, MMRV vaccines had an increased risk of fever (relative risks 1.12–1.60) and of measles/rubella-like rash (RR 1.44–1.45) [78]. Despite this increased risk of fever, a systematic review of 31 published or unpublished clinical trials involving about 40,000 subjects did not show significant differences in the incidence of febrile seizure or vaccine-related febrile seizure between MMRV and MMR with or without varicella vaccine after any doses, in the risk windows of 0–28, 0–42 or 0–56 days and 7–10 days [89]. In addition, these studies showed that concomitant use of MMRV and other paediatric vaccines was not a significant predictor of febrile seizure.
In eight post-marketing observational studies involving more than 3,200,000 subjects, there was no evidence of an elevated risk of febrile seizure associated with MMRV vaccine among children aged 4–6 years during the 7–10 days or 0–42 days after vaccination. However, an approximately 2-fold increase in the risk of seizure or febrile seizure during the 7–10 days and 5–12 days after MMRV vaccination was found among children aged 10–24 months, although the highest incidence of seizure was still lower than 2.95‰ [89].
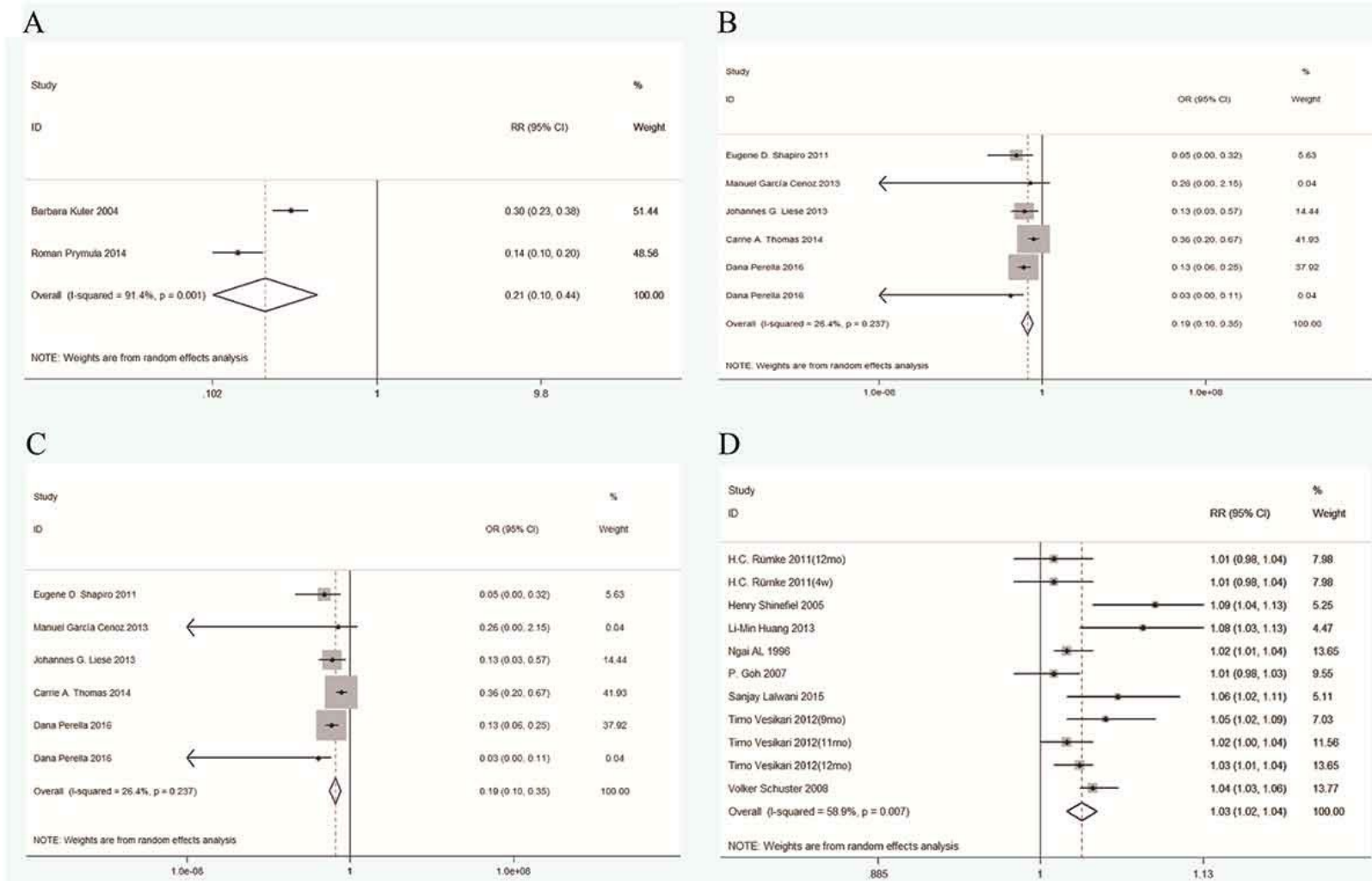
Figure 4.4 Forest plots comparing 2-dose and 1-dose varicella vaccination for (A) efficacy in randomised controlled trials, (B) effectiveness in cohort studies, by case definition, (C) effectiveness in case-control studies [82]

Although it was included in the systematic review of Ma et al. [78], we report separately on a clinical trial studying the optimal interval between consecutive doses of MMRV (Priorix-Tetra®) in 11–13-month-old children, because some of the participants were recruited in the Netherlands. The trial consisted of three groups (groups with a 4-week and a 12-month interval between two MMRV doses and a group with a 4-week interval between two doses of MMR). The incidences of pain, redness and swelling were similar in all treatment groups after both the first and the second doses. Incidences were in line with reactogenicity data assessed in the registration trials (see Section 4.4.3). The MMRV-4-weeks group had a higher observed incidence of fever of any intensity for days 0–14 after both dose 1 and dose 2 (63.9% and 44.2%) than the MMRV-12-months group (49.2% and 33.5%) and the MMR group (46.5% and 34.4%). Daily prevalence of fever of any intensity after dose 1 peaked between days 7 and 11 in all groups, which is consistent with the viraemic period of the vaccine viruses. Four febrile convulsions were reported, but none with an interval to vaccination that suggested a causal relation [79].

A randomised, double-blind clinical study with three groups - two groups receiving different dosages of Varivax® + MMR (n=206 and n=205) and one group receiving Varilrix® + MMR (n=203) - showed that vaccine-related systemic AEs occurred with similar frequencies in all three groups (23.6%, 24.5% and 19.0%, respectively). Injection-site AEs related to the varicella vaccination were reported in 17.6%–21.7%, while fever was reported in 19.1%–25.5%. Varicella-like rashes were uncommon, with frequencies of 1.0%–3.5%. Differences between the groups were not statistically significant. Only in the case of episodes of injection site swelling was the difference between the low-dose Varivax® + MMR (9.4%; 95%CI: 5.7–14.2%) and the Varilrix® + MMR groups (3.5%; 95%CI: 1.4–7.1%) statistically significant (risk difference 5.9%; 95%CI: 1.1–11.1%) [80].

In post-marketing safety studies regarding Provarivax®, including about 86,000 children aged 12 months to 12 years and 3,600 individuals of 13 years and over, no vaccine-related SAEs were reported [67].

Recently, a 22-year review of post-marketing safety data on Varivax® confirmed the safety profile found in earlier studies. In this period, more than 212 million doses were distributed globally. Varicella, rash and pyrexia were commonly reported AEs. Serious AEs comprised 0.8 reports per million doses. In 8 cases secondary transmission was reported, while 38 of the 66 reported potential secondary transmission cases were in fact attributable to wild-type VZV. The prevalence of major birth defects following inadvertent VZV vaccination during pregnancy was similar to that in the general US population. In total, 86 fatal outcomes were reported after vaccination with Varivax® (in 0.002% of 46,855 post-marketing reports), including 26 from immunocompromised patients for whom the vaccine is contraindicated. These deaths were temporally but not necessarily causally related to the vaccination. Death was associated with the following: pre-existing conditions, e.g. congenital syndromes, HIV and malignancies (n=17); complications of varicella (n=11); complications of herpes zoster (n=2); other infections (n=9); pulmonary complications (n=6); cardiac complications (n=5); CNS (n=4); and other causes (n=11); 21 reports provided insufficient information [90].

4.8 International use

A considerable number of countries all over the world have included varicella vaccination in the NIP. The overview below is based on different reviews supplemented with information from websites on immunisation schedules of the World Health Organization [91] and the European Centre for Disease Prevention and Control (ECDC) [92].

As the first country to introduce varicella vaccination, the United States started with a one-dose vaccination programme in 1996. To prevent breakthrough varicella, a second dose was added to the programme in 2006. In Canada, the implementation of universal varicella vaccination was gradual (one dose in five provinces between 2000 and 2002 and in the remaining eight provinces between 2004 and 2007) [93].

In Latin America and the Caribbean, the following countries have included varicella vaccination in their NIPs: Antigua (one dose, 2014), Argentina (one dose, 2015), Bahamas (two doses, 2012), Barbados (one dose, 2012), Bermuda (one dose, 2012), Brazil (one dose, 2013; two doses, 2018), Cayman Islands (one dose, 2000; two doses, 2009), Colombia (two doses, 2015), Costa Rica (one dose, 2007), Ecuador (one dose, 2011), Panama (two doses, 2013), Paraguay (one dose, 2013), Peru (one dose, 2018), Puerto Rico (two doses, 1997) and Uruguay (one dose, 1999; two doses, 2014) [49, 53, 83].

In the Middle East, the following countries have included varicella vaccination in their NIPs: Bahrain (two doses, 2015), Israel (two doses, 2008), Kuwait (two doses, 2017), Oman (one dose, 2010), Qatar (two doses, 2002), Saudi Arabia (two doses, 1998), Turkey (one dose, 2013) and the United Arab Emirates (two doses, 2009) [47, 54, 83].

In the Asia-Pacific region, varicella vaccination is included in the NIP in: Australia (one dose, 2005), Hong Kong (two doses, 2014), Japan (two doses, 2014), New Zealand (one dose, 2017), Niue (one dose, 2017), South Korea (one dose, 2005) and Taiwan (one dose, 2004) [45, 83].

In Europe, national policies vary between no vaccination, targeted vaccination of high-risk groups or susceptible adolescents, and universal vaccination [84, 94]. Universal varicella vaccination (publicly funded) has been implemented in: Andorra (two doses), Finland (two doses, 2017), Germany (one dose, 2004; two doses, 2009), Greece (two doses, 2006), Italy (two doses, 2017, first recommendation at regional level in 2002), Latvia (one dose, 2008; two doses, 2019), Luxembourg (two doses, 2009) and Spain (two doses, 2016; first recommendation at regional level in 2006) [83, 92, 95]. Examples of countries with recommendations for specific groups only are Belgium, Czech Republic, Poland and the United Kingdom [92].

5   Cost-effectiveness of vaccination

Several systematic reviews have been conducted on the cost-effectiveness of varicella vaccination. According to these reviews, universal varicella vaccination is expected to be cost-effective or even cost-saving from a societal perspective, when potential effects on herpes zoster incidence through diminished exogenous immune boosting are ignored. However, if these effects are incorporated, varicella vaccination is not cost-effective or cost-effective only on a very long time scale, and may even cause net health losses [96-100]. More recent cost-effectiveness analyses showed similar results [101-103].

The cost-effectiveness study tailored for the Netherlands also showed that universal childhood varicella vaccination is expected to be cost-effective or even cost-saving only if exogenous immune boosting does not play a role in the development of herpes zoster. Figure 5.1 shows the estimated impact of varicella vaccination over time on the occurrence of varicella and herpes zoster in four different scenarios at different levels of vaccination coverage. The scenarios differ by whether or not they include exogenous immune boosting, and whether or not reactivation of vaccine virus is included. The full impact of vaccination on reducing the varicella incidence occurs within 5–10 years into the vaccination programme. The potential increase in herpes zoster in the scenarios with exogenous boosting (A and C) occurs on a much longer timescale of 20–60 years. Figure 5.2 shows a stylised overview of the cost-effectiveness at high vaccination coverage (95%). In the scenarios with exogenous boosting, vaccination at high coverage is not cost-effective (scenario C) or cost-effective only in the very long term (scenario A), with the exception of the first 10 years after the start of vaccination. This exception is due to the low varicella incidence while herpes zoster incidence has not yet increased. In scenarios without exogenous immune boosting, vaccination at high coverage is expected to be cost-effective (scenario D) or even cost-saving (scenario B) [103].

Figure 5.3 shows the impact of varicella vaccination by birth cohort. The scenarios yield identical results for varicella, but differ substantially for herpes zoster. These results reveal that varicella vaccination may result in inequalities between generations. In scenarios with exogenous boosting (A and C) benefits accrue in vaccinated cohorts, while the burden and costs are largely due to herpes zoster in unvaccinated cohorts. These results reveal a possible ethical dilemma, as groups not included in the vaccination programme may be exposed to a substantially increased health hazard. Furthermore, at high vaccination coverage a significant increase is expected in the mean age of primary infection (varicella) from 4 to almost 15 years of age in all scenarios, and even higher for some birth cohorts. At higher ages, varicella usually has a more severe course and varicella during pregnancy can lead to congenital varicella syndrome. In scenarios with exogenous boosting, the mean age of reactivation (herpes zoster) is expected to shift by almost 10 years to persons in their fifties, resulting in more productivity losses [103].

At present there is no conclusive evidence on whether or not universal varicella vaccination will lead to a temporary increase in herpes zoster. The general opinion is that exogenous immune boosting does exist, but its magnitude has yet to be determined [12, 13]. It is possible that even a modest level of endogenous boosting might diminish the projected increase in herpes zoster incidence, which may be an explanation for the divergence between real-world evidence and previous projections of herpes zoster incidence after the introduction of universal varicella vaccination [104, 105]. However, it might be too early to draw final conclusions because the possible effect on herpes zoster incidence is expected to occur several decades after the introduction of universal varicella vaccination. The United States has the longest history of universal varicella vaccination: its programme started in 1996 but the initial vaccination coverage was low and ongoing exposure to VZV is likely to have occurred until recommendation of a second dose in 2006.
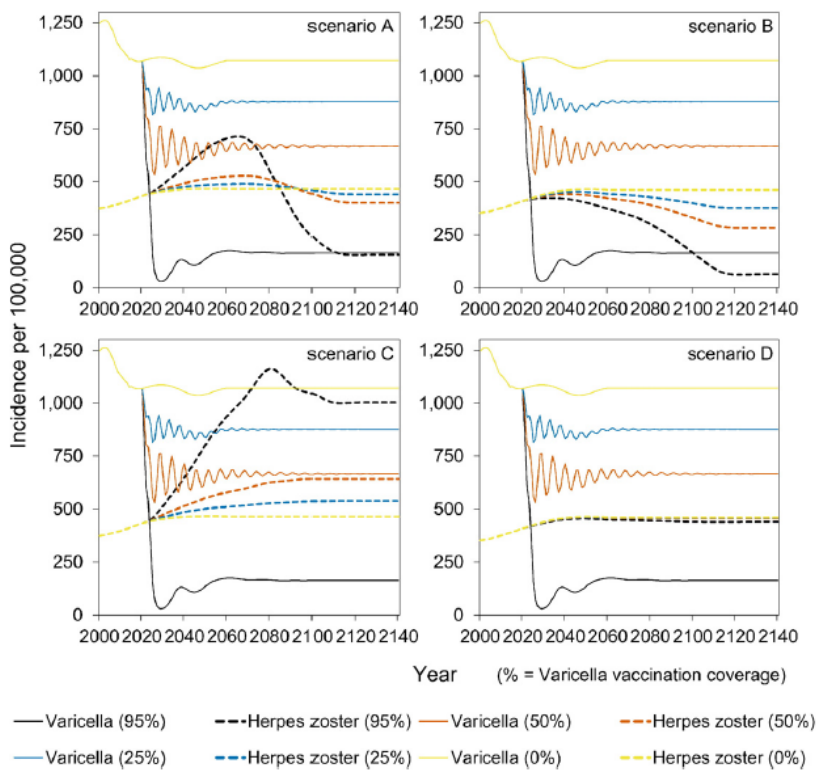

Figure 5.1 Impact of varicella vaccination over time on the occurrence of varicella and herpes zoster with a vaccination programme starting in 2020 [103]
Scenario A: with exogenous boosting, no reactivation of vaccine VZV; scenario B: without exogenous boosting, no reactivation of vaccine VZV; scenario C: with exogenous boosting, with reactivation of vaccine VZV; scenario D: without exogenous boosting, with reactivation of vaccine VZV.
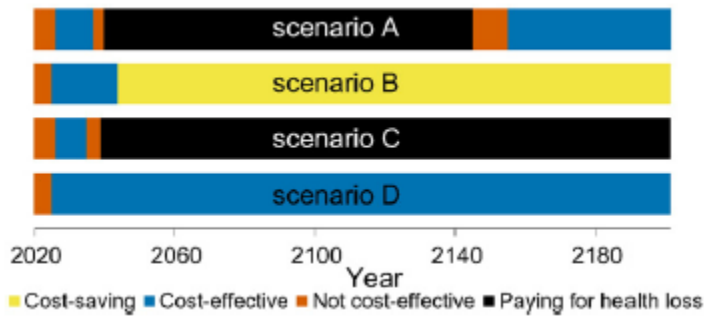
Figure 5.2 Stylised overview of the cost-effectiveness of high-coverage (95%) varicella vaccination programme over time; incremental cost-effectiveness ratio (ICER) threshold is set at €20,000 per QALY [103]
Scenario A: with exogenous boosting, no reactivation of vaccine VZV; scenario B: without exogenous boosting, no reactivation of vaccine VZV; scenario C: with exogenous boosting, with reactivation of vaccine VZV; scenario D: without exogenous boosting, with reactivation of vaccine VZV.
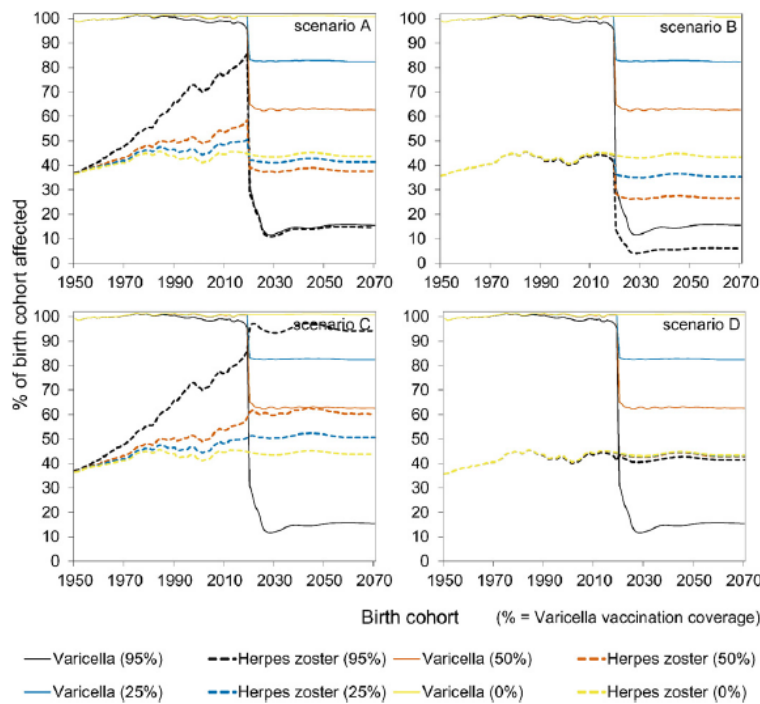

Figure 5.3 Impact of varicella vaccination by birth cohort on the occurrence of varicella and herpes zoster with a vaccination programme starting in 2020 [103]
Scenario A: with exogenous boosting, no reactivation of vaccine VZV; scenario B: without exogenous boosting, no reactivation of vaccine VZV; scenario C: with exogenous boosting, with reactivation of vaccine VZV; scenario D: without exogenous boosting, with reactivation of vaccine VZV.

6 Acceptance of vaccination

6.1 Acceptance of vaccination in the Netherlands

In the Netherlands, several questionnaire studies have been conducted on the acceptance of new vaccinations, including varicella vaccination, among public health professionals and the public. In a study conducted in 2003/2004, Van de Bovenkamp-Meijer and Rümke found that 39% of Dutch parents had a positive intention towards varicella vaccination, whereas 54% were unwilling to vaccinate their child against varicella [106]. Harmsen et al. found a positive intention among 43% of parents (unpublished data) and showed that vaccine providers perceived varicella vaccination as less important than vaccination against meningococcal B disease, respiratory syncytial virus and rotavirus [107].

Two more recent internet surveys among professionals and parents in the Netherlands showed that 21% of public health professionals had a positive attitude toward universal varicella vaccination, whereas 72% preferred to limit varicella vaccination to groups at high risk of severe varicella or susceptible adolescents; and 28% of parents with young children had a positive intention to vaccinate their child(ren) against varicella if vaccination were offered in the NIP setting. Both professionals and parents did not consider varicella to be a serious enough disease to require prevention by vaccination [108]. The percentage of parents with a positive intention to vaccinate against varicella (28%) was lower than for rotavirus gastroenteritis (38%) and much lower than for meningococcal B disease (83%), but higher than for seasonal influenza (15%) [109].

Previous research showed that public health professionals who carry out the NIP play a crucial role in influencing parents' decision to vaccinate their child(ren) [110, 111]. As they inform parents about the importance of vaccination and deal with their critical questions, they would need to support varicella vaccination, if it were to be introduced.

6.2 Acceptance of vaccination in other countries

National data on varicella vaccination coverage are not easy to collect and are often difficult to compare due to differences in vaccination schedules, estimation methods, date of start of the programme, etc. This section focuses on vaccination coverage in the United States (the country with the longest history of varicella vaccination) and Germany (country neighbouring the Netherlands).

In the United States, national vaccination coverage among children aged 19 to 35 months increased to 89% in the period 1996–2006 (1-dose programme) [60]. The coverage for ≥1 dose of varicella vaccine has been maintained at 90–92% since 2007 and was 91% in 2017 (Figure 7.1) [112, 113]. Two-dose varicella vaccination coverage among children aged 7 years increased from a range of 3.6–8.9% in 2006 to a range of 79.9–92.0% in 2012 according to six sentinel sites [114]. It should be noted that vaccination is obligatory at school-entry, partly explaining the high coverage.
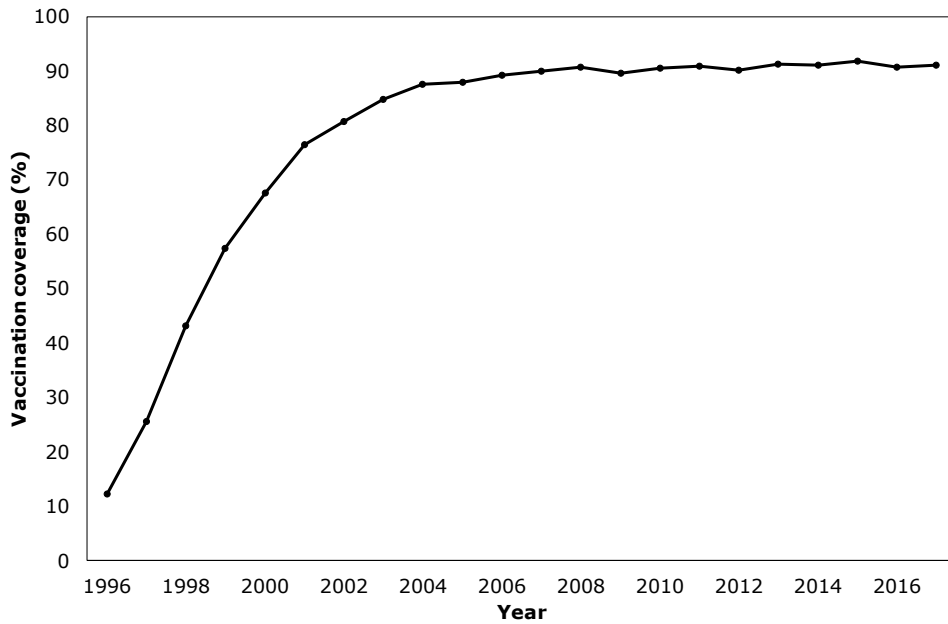
Figure 7.1 Vaccination coverage ≥1-dose varicella vaccination among children aged 19–35 months in the United States, by year [113]

In Germany, varicella vaccination coverage at 24 months of age increased for the birth cohort 2004–2009 from 43% to 87% for one dose and from 1% to 64% for two doses [115]. Another study showed that coverage for the first dose increased in the period 2009–2011 from 53% to 69% in Munich and from 72% to 83% in Würzburg [116]. More recent data showed an increase to 87.3% for one dose and to 83.7% for two doses in 2017 (Figure 7.2) [117].
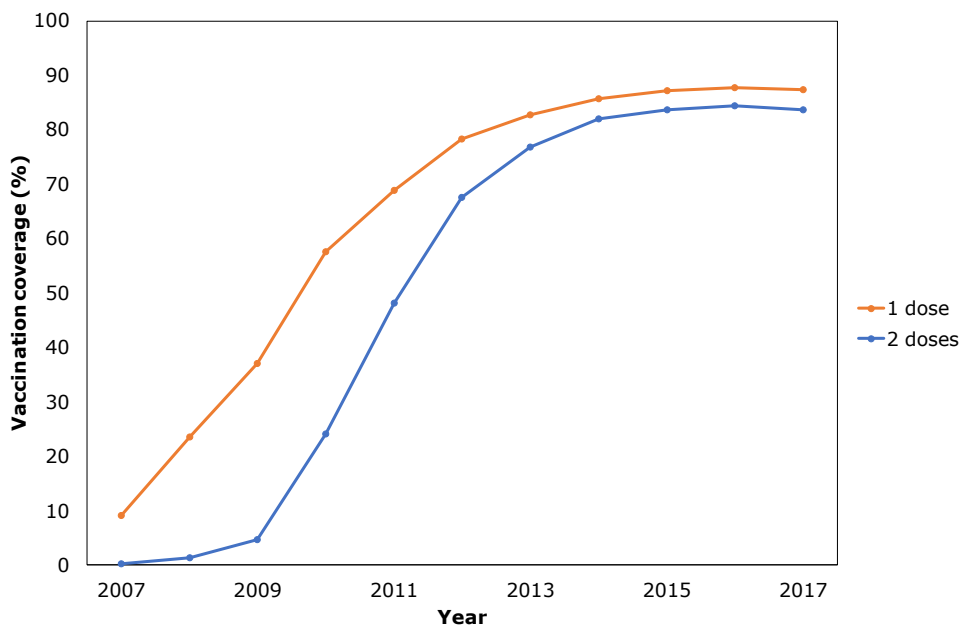

Figure 7.2 Varicella vaccination coverage at school entrance in Germany, by year [117]

7 Aspects of implementation

Today, hardly any varicella vaccinations are prescribed or administered in the Netherlands. Varicella vaccination is indicated only for 1) specific medical high-risk groups (seronegative persons who will undergo immunosuppressive therapy [66], seronegative children with leukaemia at least 1 year in full remission, HIV-positive children who are seronegative, seronegative siblings of children who will undergo chemotherapy, and seronegative women with a pregnancy wish) and 2) those with an occupational risk (seronegative individuals who work with patients at a high risk of severe varicella and seronegative individuals working with young children) [118]. An updated guideline on varicella from the Dutch Association for Medical Microbiology (NVMM) is expected in 2020. Although universal varicella vaccination is currently not in place in the Netherlands, parents can decide to vaccinate their child against varicella at their own expense. For this purpose, information on varicella vaccination for professionals (factsheet) and the public (Q&A) is available from the RIVM website (developed as part of the project 'Vaccinatie op maat').

In the Netherlands, nearly everyone is affected by VZV sooner or later. The disease burden of varicella in the Netherlands is relatively low, probably due to the low age of infection. Note, however, that in the Caribbean Netherlands the average age of infection is considerably higher (see Chapter 3).

At this moment, one monovalent varicella vaccine (Provarivax®) and two MMRV vaccines (ProQuad® and Priorix-Tetra®) are licensed and available in the Netherlands. The indication differs by vaccine. MMRV vaccine is associated with a higher risk of fever and febrile seizures than MMR+V vaccine [119]. To prevent breakthrough varicella, two doses of varicella vaccine are more effective than one, and a period of 3–4 years between the first and second doses may achieve higher efficacy [81, 82, 120]. In the current Dutch immunisation schedule, the time interval between the two MMR vaccinations - recommended at 14 months and 9 years of age - is longer. It should be noted that the Health Council will evaluate the whole NIP scheme, including the timing of the MMR vaccinations, in 2021 [121]. The vaccine virus can also reactivate and cause herpes zoster, although this is expected to be less common than after natural VZV infection. As all varicella vaccines are live-attenuated vaccines, they are contraindicated in the immunocompromised, whereas these people are at higher risk of severe infection (see Chapter 4).

The cost-effectiveness of universal varicella vaccination depends greatly on whether or not diminished exogenous immune boosting will lead to a temporary increase in herpes zoster. If Hope-Simpson's hypothesis [11] is valid, varicella vaccination will not be cost-effective and may even cause health loss. However, at present there is no conclusive evidence on whether or not universal varicella vaccination will lead to a temporary increase in herpes zoster (see Chapter 5).

From a public health perspective, high vaccination coverage is essential for the successful implementation of varicella vaccination. The World Health Organization advises that it is necessary to reach a sustained vaccination coverage of at least 80% in order to avoid a possible age shift in the peak incidence of varicella due to vaccination. Moderate vaccination coverage levels (30–70%) over the long term may increase varicella-related morbidity and mortality [122]. Vaccination coverage of at least 94.1% (95%CI: 91.3–95.9%) [40] is estimated to be necessary to achieve herd protection in the Netherlands, i.e. to eliminate endemic VZV transmission and to prevent the formation of an unvaccinated population at risk of delayed infection, and hence more severe disease, at an older age. Research among public health professionals and parents in the Netherlands showed a positive attitude and intention regarding varicella vaccination lower than the ≥80% advised by the World Health Organization (see Chapter 6).

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