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

Herpes zoster in the Netherlands

Background information for the Health Council

RIVM Report 2018-0110

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Synopsis

Herpes zoster in the Netherlands
Background information for the Health Council

Herpes zoster (also known as shingles) is caused by infection with the varicella zoster virus which can also cause varicella (also known as chickenpox). After primary infection (varicella), the virus remains inactive in the recipient's body. If, at a later stage, the virus becomes active, it can cause herpes zoster.

In the Netherlands, the Minister of Health, Welfare and Sport (VWS) determines which vaccinations are offered nationally. The minister takes this decision based on advice from the Health Council. The Health Council is currently preparing a new advice regarding herpes zoster vaccination. In 2016, herpes zoster vaccination with the then available vaccine Zostavax® did not qualify for a national programme as the vaccine did not provide sufficient protection. According to the Health Council, the vaccination could be reconsidered as soon as a new vaccine became available. This was the case at the beginning of 2018 (Shingrix®).

To support the Health Council's advisory report, the RIVM collected background information about vaccination for herpes zoster and the extent to which it occurs in the Netherlands. These overviews are created when the Health Council prepares an advisory report about a possible new vaccination. This document includes information about the number of people in the Netherlands who become ill every year, the efficacy and safety of vaccines, and the opinion of the public about vaccination for herpes zoster.

Herpes zoster usually starts with itching, tingling or severe, burning or stabbing pain. After a few days, groups of vesicles appear on the body, usually around the abdomen or waist. After 10 to 14 days, the vesicles dry to crusts. Sometimes herpes zoster can cause serious complications, such as nerve pain (postherpetic neuralgia or PHN) or inflammation of the facial nerve. Nerve pain can persist after the vesicles have disappeared, sometimes for a long time. People rarely die from herpes zoster. The chance that someone gets herpes zoster is 23 to 30 percent; it is most common in adults aged over 50.

Keywords: herpes zoster, shingles, vaccination, disease burden, cost-effectiveness, safety, acceptance

Publiekssamenvatting

Gordelroos in Nederland

Achtergrondinformatie voor de Gezondheidsraad

Gordelroos wordt veroorzaakt door een infectie met het varicellazostervirus. Dit virus veroorzaakt ook waterpokken. 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 landelijk worden aangeboden. De minister neemt die beslissing op basis van een advies van de Gezondheidsraad. Momenteel bereidt de Gezondheidsraad een nieuw advies voor over vaccinatie tegen gordelroos. In 2016 kwam vaccinatie tegen gordelroos met het toen beschikbare vaccin Zostavax® niet in aanmerking voor een landelijk aanbod. Het vaccin bood onvoldoende bescherming. Volgens de Gezondheidsraad zou de vaccinatie opnieuw kunnen worden overwogen zodra er een nieuw vaccin op de markt zou komen. Dit was begin 2018 het geval (Shingrix®).

Als ondersteuning van het advies door de Gezondheidsraad heeft het RIVM achtergrondinformatie verzameld over vaccinatie tegen gordelroos en de mate waarin het in Nederland voorkomt. Zo'n overzicht wordt gemaakt wanneer de Gezondheidsraad een advies over een mogelijke nieuwe vaccinatie voorbereidt. Het document bevat onder meer informatie over het aantal mensen in Nederland dat jaarlijks ziek wordt, de werkzaamheid en veiligheid van vaccins en de mening van het publiek over gordelroosvaccinatie.

Gordelroos begint meestal met jeuk, tintelingen of hevige, brandende of stekende pijn. Na enkele dagen verschijnen groepen blaasjes op het lichaam, meestal rond de buik of taille. Na tien tot veertien dagen drogen de blaasjes in tot korstjes. Soms kan gordelroos ernstige complicaties veroorzaken, zoals zenuwpijn (postherpetische neuralgie of PHN) of een ontsteking van de aangezichtszenuw. Zenuwpijn kan aanhouden nadat de blaasjes zijn verdwenen, soms zelfs lange tijd. Mensen overlijden zelden als gevolg van gordelroos. De kans dat iemand in zijn leven gordelroos krijgt is 23 tot 30 procent. Het komt vooral voor bij volwassenen die ouder zijn dan 50 jaar.

Kernwoorden: gordelroos, herpes zoster, vaccinatie, ziektelast, kosteneffectiviteit, veiligheid, acceptatie

Contents

1 Background

Herpes zoster (HZ) is caused by the varicella zoster virus (VZV). Primary infection leads to varicella (also called chickenpox), whereas HZ (also called shingles) is caused by reactivation of latent VZV in sensory nerve ganglia. In contrast to varicella, which is mainly a childhood disease, HZ predominantly affects adults aged 50 years and older [1, 2]. The lifetime risk of HZ has been estimated at 23-30%; approximately 50% of all people reaching the age of 85 will have experienced HZ [3]. HZ is characterised by a painful vesicular dermatomal rash, and postherpetic neuralgia (PHN) is the most common complication [4]. Because therapeutic options for HZ and especially PHN are scarce [2], prevention by vaccination might be valuable.

In 2016, the Health Council of the Netherlands concluded that vaccination against HZ, with the only available live attenuated vaccine Zostavax® (ZVL), was not eligible for inclusion in a public programme such as the National Immunisation Programme. This is because HZ does not spread in a way that might pose a threat to the health of the population or that might be an impediment to the fabric of society, and it is not an epidemic disease. Furthermore, the effectiveness and duration of the protection of Zostavax® was considered limited, and the vaccine is unsafe for immunocompromised people. The Health Council noted that it might be useful to reconsider vaccination against HZ should a new vaccine (not containing living virus), that was under development at that time, become available [5].

The 2016 advice of the Health Council was fully based on Zostavax® and the somewhat lower incidence estimates for HZ in the years 2002-2011 due to a later change in methodology (see section 3.2). Recently, the new non-live recombinant subunit vaccine Shingrix® (RZV) has been released on the market. Given the availability of this new vaccine and more up-to-date incidence estimates using a new method, there is a need to reconsider whether or not vaccination against HZ is desirable in the Netherlands.

In this report, we present the most recent scientific information available on HZ in general, the burden of HZ in the Netherlands, the effectiveness, safety, acceptance, and cost-effectiveness of available vaccines against HZ, and aspects of implementation of HZ vaccination. We have structured the report according to the criteria laid down by the Health Council of the Netherlands to assess vaccinations [6].

2 Herpes zoster

2.1 Pathogen

HZ 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 HZ, most common in older adults [1, 2].

2.2 Transmission

VZV is highly contagious and is transmitted by air as droplet spread from the pharynx or from aerosols from skin lesions of a case with varicella or HZ [2]. However, HZ is not transmitted directly; it is a reactivation of VZV that remains latent in sensory nerve ganglia after primary infection (varicella). Therefore, HZ does not occur in epidemics and periodicity is not described. However, the herpes lesions are contagious for non-immune persons and can lead to varicella (primary infection) [2, 7, 8]. Due to the fact that HZ is most common in older adults – VZV seroprevalence in the Netherlands at that age is high (Figure 2.1) and HZ lesions occur very locally – this mode of transmission is expected to be very limited.

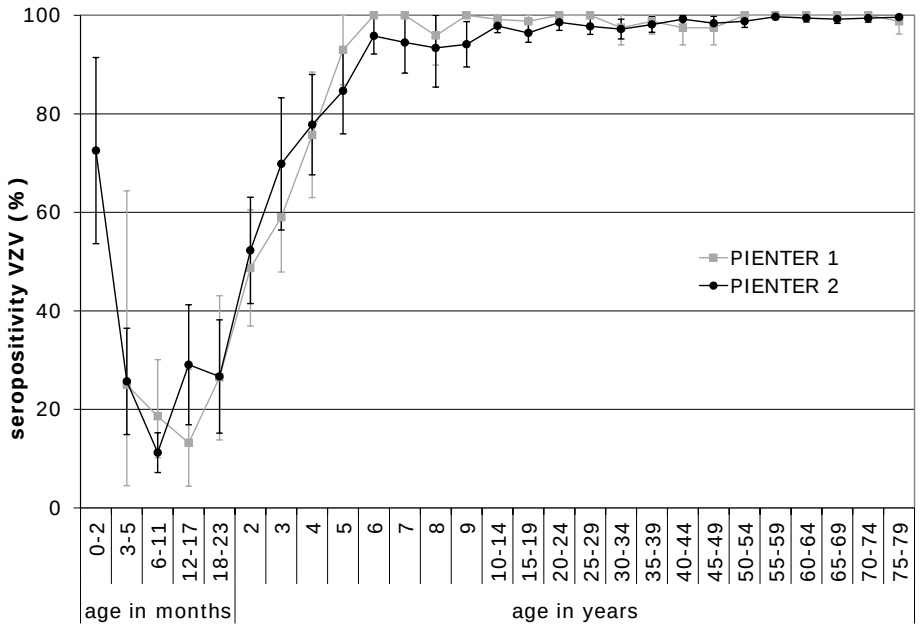

Figure 2.1 Age-specific seroprevalence for varicella zoster virus (VZV) specific antibodies, with 95% confidence intervals – PIENTER 2 (2006/2007) versus PIENTER 1 (1995/1996) [9, 10]

2.3 Symptoms and outcomes

HZ is a localised disease characterised by unilateral radicular pain and a vesicular eruption (rash). HZ usually starts with itching, tingling or intense, burning or stabbing pain [4]. After a few days, vesicles appear in groups on the body which dry to crusts after 10 to 14 days [2]. These vesicles are generally limited to the dermatome innervated by a single spinal or cranial sensory ganglion and occur most often in dermatomes innervated by the ophthalmic division of the trigeminal ganglion (between 8% and 15%) and by spinal sensory ganglia from T1 to L2 (more than 50%) [4].

PHN, pain which in some cases can persist for months or even years beyond rash healing, is seen as the most common complication of HZ. The underlying cause of PHN is damage to neural tissues caused by VZV replication; overall incidence is estimated at 9-15%. Another common sequelae of HZ is anaesthesia in the affected dermatome. On rare occasions, HZ can cause facial paralysis. Except for PHN and complications of ophthalmic HZ, serious complications of HZ occur predominantly in immunocompromised patients [4].

2.4 Diagnostics

HZ diagnosis is mostly determined clinically. HZ complaints are highly specific and accompanied by typical lesions, with a positive predictive value of clinical judgment estimated at 90.8% (95%CI: 87.3-94.3%) [11].

There are different techniques for laboratory diagnosis of VZV infection examining specimens of skin scrapings from the base of vesicular lesions and vesicular fluid. VZV can be identified by culture, or indirectly by PCR or rapid antigen test based on immunofluorescence techniques. Electron microscopy can be used to identify individual herpesviruses in situations in which rapid diagnosis is needed (e.g., to rule out suspected smallpox), and when antigen detection methods are not available. The Tzanck smear is a rapid and useful test for confirmation of an α-herpesvirus infection but is not specific for VZV. The fluorescent antibody to membrane antigen (FAMA) test is regarded as the gold standard serological test for identification of VZV antibodies [1, 12].

2.5 Treatment

Besides prevention by vaccination, therapeutic options for the acute phase of HZ and especially PHN are scarce. About half of the patients with PHN will benefit from therapy with only partial relief. The acute phase of HZ can be treated (preferably within 72 hours after rash onset) with nucleoside analogues (e.g., acyclovir, valacyclovir or famciclovir), antiviral drugs that inhibit VZV replication. However, their use is suboptimal because of delay of the diagnosis (not all patients present in time to benefit from therapy), and their effect on PHN is controversial. Additional treatment in the acute phase often requires the use of strong analgesics for pain. Significant PHN often requires multiple drugs.
In immunocompromised patients, the prime consideration is to prevent morbidity and mortality associated with visceral dissemination of VZV [2, 13].

2.6 Risk factors

Risk factors do not offer any leads for effective prevention of HZ or a risk group policy; the percentage affected by the disease is too high and the risk factors mentioned are too difficult to be influenced or cannot be influenced at all.

Nearly everyone encounters the varicella zoster virus (VZV) in early life [9] (Figure 2.1) and consequently is also at risk of virus reactivation later in life, resulting in HZ. The latency mechanism is not fully understood but reactivation of VZV is thought to result from waning of cell-mediated immunity (VZV-CMI) – and not from waning of VZV specific antibodies – over time [2]. This may be due to waning of VZV specific immunity with increasing time following primary infection, or to generalised decay in cell-mediated immunity that occurs with age (immunosenescence) [14].

Hope-Simpson hypothesised that VZV immunity can be boosted in two ways: (1) exogenous boosting by contact with a person experiencing varicella, and (2) endogenous boosting by a reactivation attempt of the virus [15]. Childhood varicella vaccination will change varicella exposure in the population, theoretically reducing immune boosting and possibly shifting the age of onset of HZ in latently infected adults, resulting in an increase in HZ in the mid-term [16]. If so, programmatic HZ vaccination could be considered to mitigate this effect. On the other hand, childhood varicella vaccination may reduce HZ incidence or complications in the long term by preventing primary wild type VZV infection, assuming latent vaccine VZV virus is less likely to reactivate or cause HZ complications when it does reactivate [8].
Currently, the effects of immune boosting remain uncertain. Although there are reports of increasing HZ incidence in populations with childhood varicella vaccination [17, 18], the time since the introduction of vaccination has probably been too short to draw definitive conclusions. Furthermore, long-term evidence on vaccine VZV reactivation is still limited. A recent transmission modelling study showed that models with high levels of exogenous boosting and low or zero endogenous boosting, constant rate of loss of immunity, and reactivation rate increasing with age give the best fit to the epidemiological data of VZV [19]. A modelling study by Ogunjimi et al. estimated the duration of exogenous boosting after re-exposure to VZV to be limited to one or two years, and that endogenous boosting has no significant effect [20].

The most important risk factors for HZ are increasing age and a compromised immune system [14]. Although HZ can affect people of all ages, the majority of patients occur in the elderly (sharpest increase in incidence is around 50-60 years) and therefore age – i.e., the senescence of cellular immune responses to VZV that occurs with increasing age – is seen as the most important risk factor for HZ. Childhood zoster is a much milder disease in immunocompetent children than HZ in adults (absence of chronic pain) and primary VZV infection of the mother during pregnancy or the child during the first year of life increases susceptibility to HZ during childhood and adulthood [8, 14].

In comparison with immunocompetent individuals, the incidence and severity of HZ are increased in patients with supressed cell-mediated immunity (patients with HIV/AIDS, certain cancers, organ transplants, immune-mediated diseases and immunosuppressive treatments) [8].

Some studies (including a Dutch study) found an increased risk of HZ in females compared to males, however others did not [8, 14, 21]. Women might be more likely to seek medical advice, may have increased prevalence for risk factors or might be more susceptible due to some biological mechanism [14]. Race and country of birth might also be risk factors: non-whites and people born in (tropical) countries with late-onset varicella are less likely to have experienced zoster than white people [8, 14]. Psychological stress, exposure to immunotoxic chemicals, cytomegalovirus (CMV) infection (generalised suppression of cell-mediated immunity), mechanical trauma and genetic susceptibility could also be potential risk factors for HZ [14, 22]. However, it is possible that some of these factors are determinants of immunosenescence itself.

Risk factors for PHN

The most important risk factor for PHN is age: PHN is rare in HZ patients aged <40 but occurs in more than 50% of HZ patients aged >60. Other risk factors are intensity of prodromal pain, intensity of acute pain, HZ involving cranial nerves (as opposed to thoracic or lumbar HZ), severity and extent of the rash, and immunosuppression [2, 4, 23]. Furthermore, greater VZV CMI responses in the first week after HZ rash onset correlated with decreased disease severity and with lower occurrence of PHN, suggesting a protective effect of CMI against the morbidity of HZ [24].

3 Epidemiology of herpes zoster

The lifetime risk of HZ has been estimated at 23-30%; approximately 50% of all people reaching the age of 85 will have experienced HZ [3]. In immunocompetent individuals, the frequency of recurrent HZ is low (1.7-5.2%) [3]. Due to population aging and the increasing usage of immunosuppressive therapies, the incidence of HZ is expected to increase in the future [14, 25, 26]. There are no data that indicate that the incidence of HZ differs significantly by geographic region, and cases tend to occur sporadically throughout the year without a seasonal pattern [8].

3.1 Surveillance of herpes zoster in the Netherlands

In the Netherlands, HZ is not a notifiable disease. Therefore, estimates of the incidence and disease burden of HZ are based on primary care data from a large sentinel network of general practitioners from 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 Herpes zoster incidence in the Netherlands

The incidence of HZ in the Netherlands is based on general practitioner (GP) data. It is expected that the majority of HZ patients consult their GP because it is a painful condition. Because HZ complaints are highly specific and accompanied by typical lesions, with a positive predictive value of clinical judgment estimated at 90.8% (95%CI: 87.3-94.3%), misclassification of the diagnosis by the GP is expected to occur infrequently [11, 27].
The incidence of HZ per 100,000 population based on GP data is fairly stable (Table 3.1). According to a new*, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards [28, 29], the incidence of HZ (~520 GP episodes per 100,000 population in the period 2012-2016) is higher than it was according to the old method (~340 GP episodes per 100,000 population in the period 2002-2011). The incidence among women is somewhat higher than among men (~600 versus ~440 GP episodes per 100,000 population in the period 2012-2016). Figure 3.1 shows that HZ is most common in older adults (≥50 years). Two other Dutch studies found an incidence of GP consultations due to HZ of 475 per 100,000 (95%CI: 406-544) in the period 2004-2008 (340 per 100,000 when only ICPC codes were analysed) [30], and 340 per 100,000 (95%CI: 290-390) in the period 1994-1999 [31]. The incidence of hospitalisations and deaths due to HZ per 100,000 population is also stable, with the exception of hospital admissions for one day which have decreased (Table 3.2-3.4).

* The above-mentioned new method uses constructed episodes of illness (episodes are closed after 16 weeks without a reconsultation of the GP for HZ), based on an algorithm instead of the recorded 'raw' episodes of care 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').

3.3 Morbidity and mortality due to herpes zoster in the Netherlands

Based on the mean incidence in 2012-2016, the GP was visited for ~88,000 episodes of HZ annually (~55,000 in the period 2000-2011 based on the old method). The risk of PHN (3 months after HZ diagnosis) has been estimated at 3-19% for Dutch older adults and increases with age [31, 32]. In the period 2000-2014, ~370 patients were hospitalised with main diagnosis HZ annually, and at the end of this period an additional 600 admissions for one day were observed. Annually, ~20 HZ-associated deaths were reported in the period 2000-2017. However, it is unlikely that death was caused directly by HZ. Therefore, a vaccination programme is expected to only prevent some of these deaths.

Mahamud et al. found that national death certificate data tend to overestimate the number of deaths in which HZ is the underlying or contributing cause of death. They found that that most decedents for whom HZ was determined not to be the underlying or a contributing cause of death had a history of HZ in the medical record, but did not have active disease that resulted in or contributed to death [33]. If we apply their rate of deaths for which HZ was validated as the underlying cause of death (0.25 (range 0.10-0.38) per 1 million population) to the Dutch population in 2017, we would expect 4.3 deaths (range 1.7-6.5) instead of the 33 deaths reported in 2017.

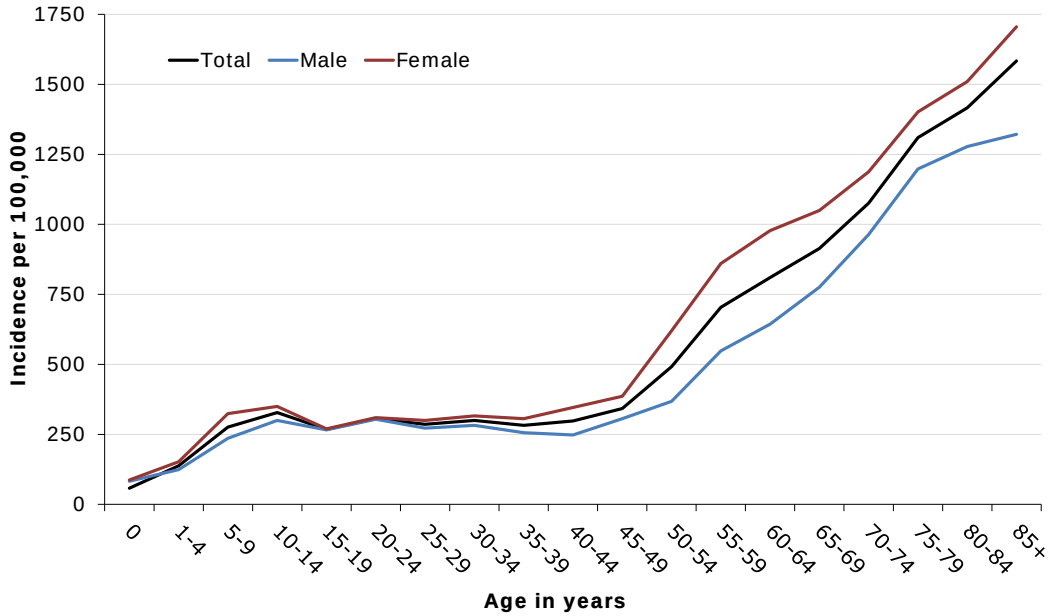

Figure 3.1 Estimated incidence per 100,000 population of episodes of herpes zoster (ICPC-code S70) in 2012-2016, by age group [28]

Source: NIVEL

3.4 Burden of disease of herpes zoster 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. Kristensen et al. estimated the burden of HZ among people aged 50 and older in the period 2010-2013 at 942 (95%CI: 906-980) DALYs per year [34]. Van Lier et al. estimated the total population

burden of HZ for all ages in 2017 at 1,700 (95%UI: 1,600-1,700) DALYs; 64% in people aged 50 and older (unpublished results). In both estimates, incidence data according to the new NIVEL method were used (see section 3.2).
According to the estimates among people aged 50 and older made by Kristensen et al., the disease burden for pneumococcal disease (especially when including non-invasive disease) and influenza was higher than for HZ and pertussis [34].

3.5 Herpes zoster incidence in other countries

The incidence of HZ in community dwelling populations ranges from 1.2-3.4 per 1000 person-years, and in the elderly (aged above 65) from 3.9-11.8 per 1000 person-years. Among immunosuppressed patients, the incidence is substantially higher [8]. A review by Thomas and Hall found a comparable HZ incidence: 1.2-4.8 per 1000 person years [14]. Studies in Canada, Israel, Japan, Taiwan and the USA reported age-adjusted HZ incidence ranging from 3.4-5.0 per 1000 person-years in the total population (8-11 per 1000 person-years over the age of 65) [35]. Pinchinat et al. found similar HZ incidences across different countries in Europe (varying from 2.0-4.6 per 1000 person-years, with no clearly defined geographic trend), increasing with age, and quite drastically for those aged above 50 [36].
The incidence of HZ-associated mortality is more heterogeneous but generally low and it increases with age [37].

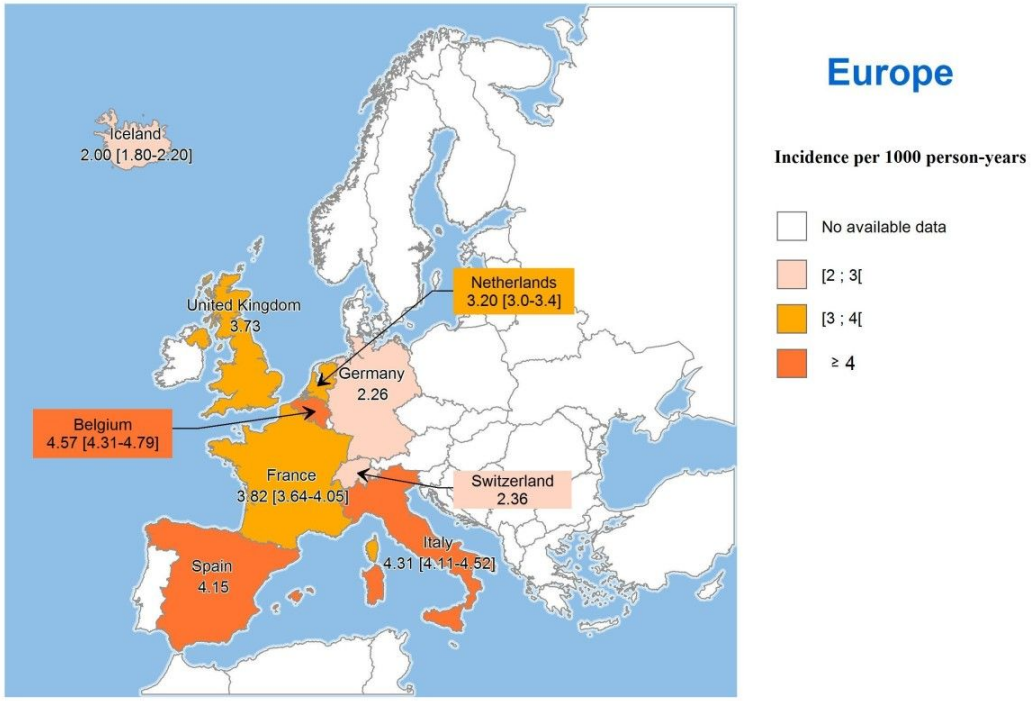

Figure 3.2 Overall annual herpes zoster incidence rates in Europe per 1000 person-years [36]
Notes: The confidence interval is presented when available in the original publication. In case of several publications per country, the publication with the most recent data and that reported the overall HZ incidence rate is depicted.

Table 3.1 Estimated incidence per 100,000 population of episodes of herpes zoster (ICPC-code S70), based on the NIVEL Primary Care Database (NIVEL-PCD), using the old method (2002-2011) and the new method (2010-2016) (rounded off to closest ten) [38]

GP consultation	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Incidence per 100,000*	320	330	310	350	370	310	340	360	360	360					
- men	*250*	*270*	*250*	*300*	*310*	*240*	*300*	*300*	*300*	*320*					
- women	*390*	*390*	*370*	*390*	*420*	*380*	*370*	*420*	*430*	*400*					
Incidence per 100,000, new**									480	490	510	510	530	530	530
- men									*390*	*420*	*420*	*430*	*450*	*450*	*440*
- women									*570*	*570*	*610*	*580*	*610*	*610*	*610*

* NIVEL-PCD, old method [39], ** NIVEL-PCD, new method from 2012 onwards [28]; 2010-2011 recalculated.
Source: NIVEL

Table 3.2 Absolute number and incidence per 100,000 population of hospitalisations (clinical admissions, admissions for one day excluded) due to main diagnosis of herpes zoster (ICD-10 code B02), 2000-2014 [40]

Clinical admission	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Absolute number	363	399	442	354	409	359	317	326	323	389	352	360	347	351	451
- men	*153*	*151*	*190*	*142*	*167*	*158*	*137*	*148*	*132*	*160*	*149*	*160*	*153*	*152*	*200*
- women	*210*	*248*	*252*	*212*	*242*	*201*	*180*	*178*	*191*	*229*	*203*	*200*	*194*	*199*	*251*
Incidence per 100,000	2.3	2.5	2.7	2.2	2.5	2.2	1.9	2.0	2.0	2.4	2.1	2.2	2.1	2.1	2.7
- men	*1.9*	*1.9*	*2.4*	*1.8*	*2.1*	*2.0*	*1.7*	*1.8*	*1.6*	*2.0*	*1.8*	*1.9*	*1.8*	*1.8*	*2.4*
- women	*2.6*	*3.1*	*3.1*	*2.6*	*2.9*	*2.4*	*2.2*	*2.2*	*2.3*	*2.7*	*2.4*	*2.4*	*2.3*	*2.3*	*3.0*

Notes:
1. In 2006/2007, a number of hospitals stopped their registration causing an underestimation of hospital admissions from 2006 onwards.
2. The number of admissions can be higher than the number of hospitalised patients reported here because some patients are admitted more than once within the same year.
3. Hospitalisation data from 2015 onwards is not yet available.

Source: DHD

Table 3.3 Absolute number and incidence per 100,000 population of admissions for one day due to main diagnosis of herpes zoster (ICD-10 code B02), 2000-2014 [40]

Admission - one day	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Absolute number	955	1,034	1,205	1,196	1,160	1,034	869	647	807	787	737	791	711	670	583
- men	*328*	*390*	*433*	*457*	*436*	*379*	*302*	*262*	*352*	*306*	*277*	*339*	*275*	*247*	*238*
- women	*627*	*644*	*772*	*739*	*724*	*655*	*567*	*385*	*455*	*481*	*460*	*452*	*436*	*423*	*345*
Incidence per 100,000	6.0	6.5	7.5	7.4	7.1	6.3	5.3	4.0	4.9	4.8	4.4	4.7	4.2	4.0	3.5
- men	*4.2*	*4.9*	*5.4*	*5.7*	*5.4*	*4.7*	*3.7*	*3.2*	*4.3*	*3.8*	*3.4*	*4.1*	*3.3*	*3.0*	*2.9*
- women	*7.8*	*8.0*	*9.5*	*9.0*	*8.8*	*7.9*	*6.9*	*4.7*	*5.5*	*5.8*	*5.5*	*5.4*	*5.2*	*5.0*	*4.1*

Notes:
1. In 2006/2007, a number of hospitals stopped their registration causing an underestimation of hospital admissions from 2006 onwards.
2. Hospitalisation data from 2015 onwards is not yet available.

Source: DHD

Table 3.4 Absolute number and incidence per 100,000 population of deaths with main cause being herpes zoster (ICD-10 code B02), 2000-2017 [41]

Death	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Absolute number	14	13	26	14	15	15	24	21	14	20	25	20	21	21	26	33	27	33
- men	*2*	*3*	*9*	*5*	*3*	*3*	*6*	*10*	*5*	*6*	*9*	*3*	*9*	*5*	*4*	*10*	*9*	*7*
- women	*12*	*10*	*17*	*9*	*12*	*12*	*18*	*11*	*9*	*14*	*16*	*17*	*12*	*16*	*22*	*23*	*18*	*26*
Incidence per 100,000	0.09	0.08	0.16	0.09	0.09	0.09	0.15	0.13	0.09	0.12	0.15	0.12	0.13	0.13	0.15	0.20	0.16	0.19
- men	*0.03*	*0.04*	*0.11*	*0.06*	*0.04*	*0.04*	*0.07*	*0.12*	*0.06*	*0.07*	*0.11*	*0.04*	*0.11*	*0.06*	*0.05*	*0.12*	*0.11*	*0.08*
- women	*0.15*	*0.12*	*0.21*	*0.11*	*0.15*	*0.15*	*0.22*	*0.13*	*0.11*	*0.17*	*0.19*	*0.20*	*0.14*	*0.19*	*0.26*	*0.27*	*0.21*	*0.30*

Source: CBS

4 Vaccines against herpes zoster

There are two vaccines available for HZ. Zostavax® is a live attenuated vaccine (ZVL; Oka/Merck VZV strain), registered in 2006 as a single dose vaccine for the prevention of HZ and PHN among immunocompetent people aged 60 and older; in 2011 extended to 50 and older [42]. In 2018, a new non-live recombinant subunit vaccine Shingrix® (RZV; VZV glycoprotein E, adjuvanted with the $AS01_B$ system which enhances $CD4^+$ T-cell responses), was registered for the prevention of HZ and PHN among people aged 50 and older in a two-dose schedule (with the second dose given 2-6 months after the first). The immunological correlates of protection for HZ are unclear; HZ occurs due to loss of cellular immunity, whereas antibodies persist [43]. Note that vaccination against HZ will only provide benefit at an individual level; no herd immunity effects are to be expected as the transmission of VZV resulting from HZ patients is very low.

4.1 Zostavax®

4.1.1 Vaccine efficacy

The efficacy of Zostavax® was assessed in a large randomised placebo-controlled trial including 38,546 adults aged 60 and older (Shingles Prevention Study, follow-up 0-4.9 years), showing a reduction of 51.3% (95%CI: 44.2-57.6%) in the incidence of HZ, 61.1% (95%CI: 51.1-69.1%) in the burden of illness (BOI) due to HZ, and 66.5% (95%CI: 47.5-79.2%) in the incidence of PHN. The vaccine appeared less effective in the older age group (70+, and especially among 80+: 18% efficacy against HZ) compared to the younger age group (60-69) (Figure 4.1), indicating that the effect of vaccination is age-dependent [44, 45].

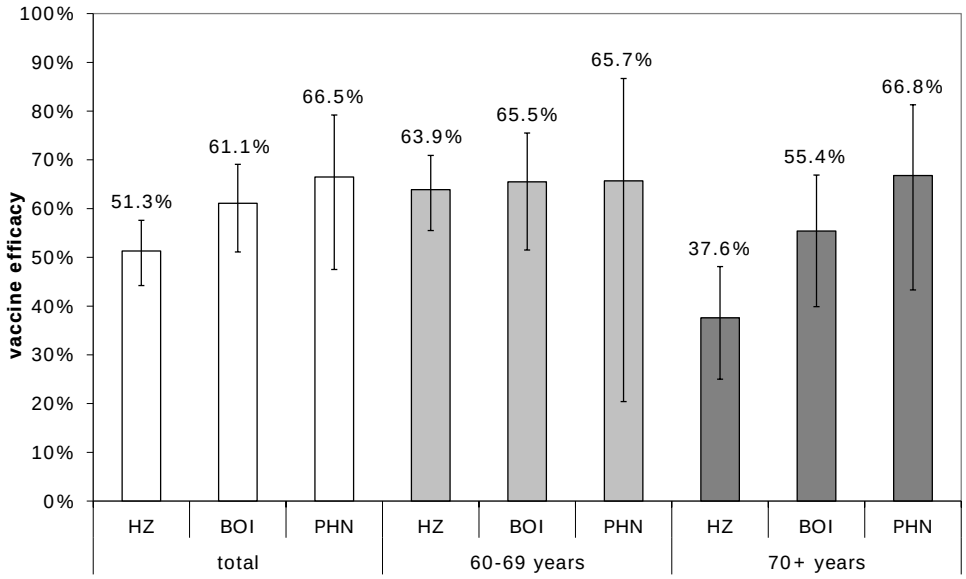

Figure 4.1 Vaccine efficacy of Zostavax® against incidence of herpes zoster (HZ), burden of illness (BOI), and postherpetic neuralgia (PHN), by age-group [44]

Among those experiencing HZ, prior HZ vaccination is associated with a lower risk of PHN in women but not in men. This sex-related difference may reflect differences in healthcare-seeking patterns [46].
An additional trial showed an efficacy against HZ of 69.8% (95%CI: 54.1-80.6%) among people aged 50-59 [47].
According to the Short-term Persistence Substudy (follow-up 3.3-7.8 years), vaccine efficacy of Zostavax® decreased from 51.3% to 39.6% for the incidence of HZ, from 61.1% to 50.1% for HZ-related BOI, and from 66.5% to 60.1% for the incidence of PHN [48].
The Long-Term Persistence Substudy (follow-up 4.7-11.6 years) showed that long-term persistence of the efficacy is limited and depends on the outcome measure: vaccine efficacy for HZ-related BOI persisted into year 10 post-vaccination, whereas vaccine efficacy for HZ incidence persisted only through year 8 (Figure 4.2). Vaccine efficacy decreased further from 51.3% to 21.1% for incidence of HZ, from 61.1% to 37.3% for HZ-related BOI, and from 66.5% to 35.4% for incidence of PHN [49].

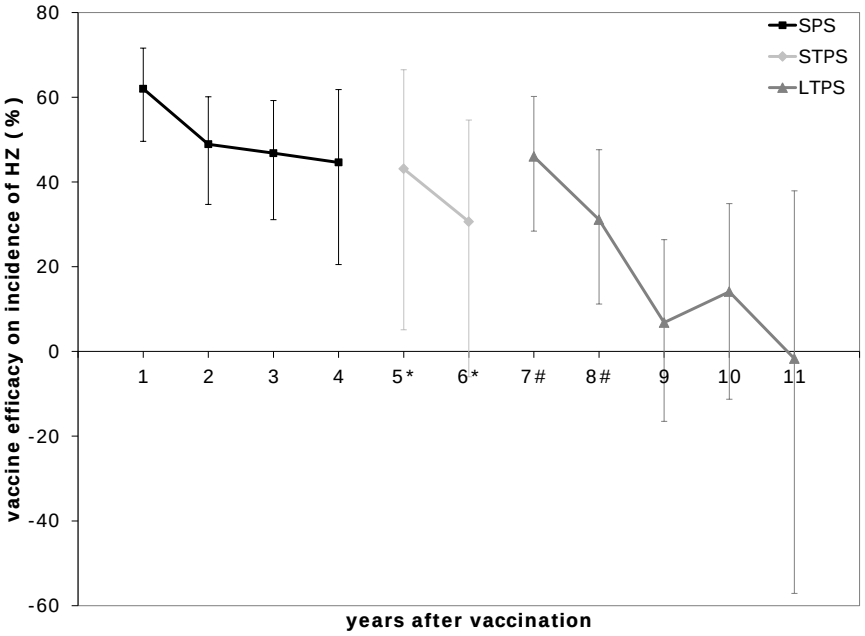

Figure 4.2 Vaccine efficacy of Zostavax® against incidence of herpes zoster (HZ) by year post-vaccination with 95% confidence intervals [49]
For year 4, person-years were 97% from Shingles Prevention Study (SPS) and 3% from Short-Term Persistence Substudy (STPS). For year 5, person years were 16% from SPS and 84% from STPS. For years 6, 100% of the events and person-years were from STPS subjects. *Data for years 5-6 from the Long-Term Persistence Substudy (LTPS) are excluded; #For years 7 and 8, both STPS and LTPS contribute vaccine group data. Vaccine efficacy in years 7 to 11 only include data from the LTPS.

4.1.2 Vaccine effectiveness

Table 4.1 presents an overview of different studies on Zostavax® vaccine effectiveness conducted in different populations in 'real-world' settings. In some of these studies, the effectiveness among the older age groups (70+ and especially 80+) was higher than the efficacy found in the original trial [44].

Table 4.1 Vaccine effectiveness of Zostavax®

Study setting, period [reference]	Population (age in years)	Follow-up period	Adjusted vaccine effectiveness (%) HZ incidence	Adjusted vaccine effectiveness (%) PHN incidence
England, Royal College of General Practitioners, 2005-2016 [50]	70-71 (routine)	First 3 years	62 (50-71)	88 (59-100)
	78-80 (catch-up)	First 3 years	62 (48-72)	70 (39-93)
United States, Kaiser Permanente Northern California, 2007-2014 [51]	All 50+	Whole follow-up period	49.1 (47.5-50.6)	
	50-59	First 3 years	59.5 (51.7-66.1)	
	60-69		54.7 (52.3-57.0)	
	70-79		49.8 (46.6-52.8)	
	80+		48.0 (42.5-53.0)	
	50-59	First 5 years	-	
	60-69		49.2 (46.8-51.5)	
	70-79		45.5 (42.5-48.4)	
	80+		43.9 (38.3-49.0)	
United Kingdom, primary health care records, 2013-2016 [52]	70-71 (routine) plus 79 (catch-up)	First 3 years	64 (60-68)	81 (61-91)
Canada, Alberta Health Care Insurance Plan Registry [53]	All 50+	First year	50.0 (44.7-54.8)	
		Fifth year	14.0 (-21.0-38.9)	
United States, Medicare database, 2007-2014 [54]	All 65+	First 3 years	33 (32-35)	57 (52-61)
	65-69		36 (33-39)	61 (49-70)
	70-74		35 (33-37)	55 (46-62)
	75-79		32 (30-34)	61 (54-68)
	80-84		31 (28-34)	55 (45-63)
	85-89		32 (27-36)	47 (27-61)
	90+		37 (29-43)	58 (22-78)
	All 65+	4 or more years	19 (17-22)	45 (36-53)
	65-69		22 (18-26)	50 (34-62)
	70-74		21 (17-24)	42 (29-53)
	75-79		17 (13-21)	50 (38-60)
	80-84		16 (11-20)	42 (26-54)
	85-89		17 (11-22)	32 (4-52)
	90+		23 (13-31)	46 (-2-72)
United States, Kaiser Permanente Southern California, 2007-2015 [55]	Immunocom-petent 60+	Up to 8 years of follow-up	49 (48-51)	
	60-64		56 (53-59)	
	65-69		48 (44-52)	
	70-74		47 (43-51)	
	75-79		47 (42-52)	
	80+		42 (36-47)	
United States, Southeastern Minnesota, 2010-2011 [56]	60+	On average 3 years after vaccination	54 (32-69)	61 (22-80) 55 (0-92) (at 30/90 days)

Study setting, period [reference]	Population (age in years)	Follow-up period	Adjusted vaccine effectiveness (%) HZ incidence	Adjusted vaccine effectiveness (%) PHN incidence
United States, Medicare database, 2007-2009 [57]	65+	Median follow-up of 6 years	48 (39-56)	62 (37-77) 59 (21-79) (at 30/90 days)
United States, Kaiser Permanente Southern California, 2007-2009 [58]	Immunocom-petent 60+ 60-64 65-69 70-74 75-79 80+	Median follow-up of 1.6 years	55 (52-58) 50 (42-57) 60 (53-66) 54 (47-61) 55 (46-62) 56 (44-65)	65 (49-76)

4.1.3 Safety

In the initial trial, the vaccine group had low rates of serious adverse events, systemic adverse events, hospitalisation and death, and these rates were similar in the placebo group. Local reactions at the vaccination site which were reported more often among the vaccine group were generally mild (erythema (35.8% versus 7.0%), pain or tenderness (34.5% versus 8.5%), swelling (26.2% versus 4.5%), and pruritus (7.1% versus 1.0%) [44].

Furthermore, during the short and long-term persistence studies no serious adverse events judged possibly, probably, or definitely related to the vaccination occurred and there was no significant difference in deaths between the vaccine and the placebo group [48, 49].

Many other studies showed that HZ vaccination in (older) adults is well tolerated and safe [47, 59-69]; it produces few systemic adverse events and injection site adverse reactions of only mild to moderate intensity [70]. Although increased risks of developing arthritis and alopecia were found after HZ vaccination, almost none of these events was life threatening. Lai et al. therefore concluded that HZ vaccine is relatively safe and unlikely to exacerbate or induce autoimmune diseases [71].

The safety profile of Zostavax®, following 10 years of post-marketing use (>34 million doses distributed worldwide), remained favourable and consistent with that observed in clinical trials and post-licensure studies; the majority (93%) of reported adverse events were non-serious, and local injection site reactions were reported most frequently [72].

Local reactogenicity was greater for subcutaneous (conventional administration), compared with intramuscular administration [73]. Transient erythema and induration were more common after intradermal administration, compared with subcutaneous administration (31% erythema for full subcutaneous dose and 77% for intradermal dose) [74].

Because of the decline in vaccine efficacy over time, the safety of a booster dose was investigated. These studies showed that a second dose of Zostavax® was also generally safe and well tolerated [63, 64, 75, 76].

4.1.4 Immunogenicity

An immunology study showed that a significant increase in VZV cell-mediated immunity and VZV antibody was induced that persisted during 3 years of follow-up, although the magnitude decreased over time [77]. Two studies showed that a second dose of Zostavax® did not increase antibody response compared to the first dose [63, 64]. In persons 50-59 years, the vaccine was also immunogenic [47, 69]; the geometric mean several fold rise of the VZV antibody response was non-inferior (i.e., not worse than) to that in subjects ≥60 years old [78].
A booster dose of Zostavax® administered to adults aged ≥70, who had received a dose of Zostavax® ≥10 years previously, elicited a VZV antibody response that was non-inferior to that of Zostavax® administered as a first dose to subjects aged ≥70 [75]. An earlier study also demonstrated the immunogenicity of a booster dose [76].

4.1.5 Specific populations

Immunocompromised population

In general, Zostavax® is contraindicated in individuals who are immunocompromised. However, the immunogenicity and safety of Zostavax® has not only been demonstrated in healthy individuals, but also in people with diabetes [79], in adults aged over 60 on chronic/maintenance corticosteroids [80], in people who have had hematopoietic stem cell transplantation [81, 82], in patients taking immuno-suppressant medications [83], in adults with hematologic malignancies receiving anti-CD20 monoclonal antibodies (using an inactivated vaccine) [84], in patients vaccinated within two years after a bone-marrow transplant [85], in patients with inflammatory and autoimmune disease [86], in patients with inflammatory bowel disease (IBD) [87, 88], in patients with rheumatoid arthritis [89, 90], in HIV-infected adults [91, 92], in patients with end-stage renal disease [93], and in patients with systemic lupus erythematosus (SLE) [94]. Results of these and similar studies in immunocompromised patients suggest that it may be time to review the current vaccination policy of excluding all immunocompromised persons [95, 96]. However, some serious reactions and vaccine-related infections were reported in immunosuppressed immune-mediated inflammatory disease or solid organ transplant patients [85]. Furthermore, different case reports described the fatality of three immunocompromised patients who received the vaccine and developed persistent disseminated HZ caused by the vaccine virus [97-99]. These cases illustrate the concerns about the use of live attenuated vaccines in immunocompromised individuals. For these patients, a subunit vaccine may be an appropriate alternative.

Adults with a prior history of HZ

Zostavax® is also immunogenic and safe in adults with a prior history of HZ [100, 101]. The risk of recurrent HZ following a recent initial episode is fairly low among immunocompetent adults, regardless of vaccination status, suggesting that immediately vaccinating after a recent HZ episode is not necessary [102].

Population in nursing homes
Zostavax® induced VZV immunity in elderly nursing home residents (aged 80-102) similar to that produced in community-dwelling seniors (aged 60-75). However, the absolute levels of VZV responses before and after vaccination were lower in the nursing home cohort than among the community-dwelling seniors. They found that higher frequencies of regulatory T-cells and cytomegalovirus-specific CD4+ T cells correlated negatively with the magnitude of VZV-specific responses. This suggests that the accumulation of these cells with age might impact vaccine responsiveness [103].

Young versus older adults
Weinberg et al. studied the VZV-specific cellular immune response of HZ vaccination in young (25-40) and older adults (60-80) and concluded that high proportions of senescent and exhausted VZV-specific T cells in the older adults contributed to their poor effector responses (lower and slower) to a VZV challenge, which may underlie their inability to contain VZV reactivation and prevent the development of HZ [104]. A recent Dutch study showed that pre-vaccination VZV specific T-cell immune responses affect vaccine induced immune responses in people aged 50-65 [105].

4.1.6 Combination with other vaccines

Kerzner et al. demonstrated that Zostavax® and inactivated influenza vaccine (IIV3) given concomitantly in adults aged 50 and older are generally well tolerated, and antibody responses were similar when Zostavax® and influenza vaccine were given concomitantly as compared to sequentially [106]. Levin showed that Zostavax® and quadrivalent inactivated influenza vaccine (IIV4) given concomitantly in adults aged 50 and older induced VZV and influenza-specific antibody responses that were comparable to those following administration of either vaccine alone, and was generally well tolerated [107].
A randomized trial that evaluated the immunogenicity of zoster vaccine and Pneumovax 23® (PPV23®) given together versus separated by at least 4 weeks demonstrated that the VZV antibody response (but not the PPV23® antibody response) of concomitant administration was inferior compared to nonconcomitant administration, while both vaccines were generally well tolerated when administered concomitantly [108]. Another study showed that Zostavax® can be used safely but it cannot boost VZV specific immunity in people with diabetes mellitus when administered concurrently with PPV23® [109]. However, a large observational study that compared the incidence of HZ following concomitant versus nonconcomitant administration of pneumococcal vaccine and Zostavax® found no evidence of an increased risk of HZ among people receiving both vaccines concomitantly [110, 111]. Therefore, to improve immunisation rates, concomitant administration is advocated in a number of countries e.g. the United States, United Kingdom, Australia, and Canada [112-115].

4.2 Shingrix®

4.2.1 Vaccine efficacy

A phase III study (ZOE-50) among 15,411 older adults (aged ≥50) in 18 countries with a follow-up period of 3.2 years, showed that the efficacy of Shingrix® (two doses administered two months apart) against HZ is high at 97.2% (95%CI: 93.7-99.0%) and does not depend on the age at administration (Figure 4.3) [116]. A randomised, placebo-controlled, phase III trial (ZOE-70) conducted in 18 countries with a mean follow-up of 3.7 years involving 13,900 adults aged 70 and older showed an efficacy of two doses of Shingrix® against HZ of 89.8% (95%CI: 84.2-93.7%). In pooled analyses of data from 16,596 participants aged 70 and older in ZOE-50 and ZOE-70, vaccine efficacy against HZ was 91.3% (95%CI: 86.8-94.5%) and against PHN 88.8% (95%CI: 68.7-97.1%). PHN did not occur among vaccinees aged <70 [117]. Efficacy against HZ-related complications was 93.7% (95%CI: 59.5-99.9%) in adults aged ≥50 and 91.6% (95%CI: 43.3-99.8%) in adults aged ≥70 [118].
Currently, the duration of protection is unknown, but trial data confirmed high efficacy up to 4 years follow-up [117]. In a study that was initially performed to assess immune persistence, no suspected HZ breakthrough episodes were reported after a follow-up period of 9 years [119]. Tricco et al. conducted a meta-analysis and concluded that Shingrix® was superior to both Zostavax® (vaccine efficacy 85%; 95%CI: 31-98%) and placebo (vaccine efficacy 94%; 95%CI: 79-98%) [120].

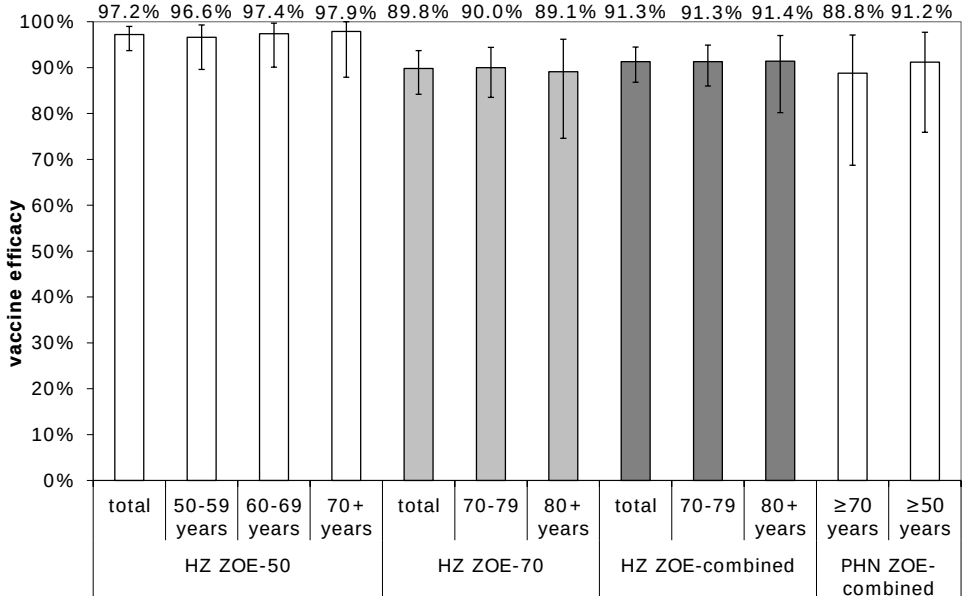

Figure 4.3 Vaccine efficacy of Shingrix® in ZOE-50 and ZOE-70 study (and both studies combined) against incidence of herpes zoster (HZ), and postherpetic neuralgia (PHN), by age-group [116, 117]

4.2.2 Vaccine effectiveness

To date, no results of effectiveness studies have been published, as Shingrix® was only registered in 2018.

4.2.3 Safety

In the reactogenicity subgroup of the initial trial (ZOE-50), solicited or unsolicited symptoms within 7 days after vaccination were reported in 84.4% in the vaccine group compared to 37.8% in the placebo group. Most symptoms were mild to moderate and transient but 17.0% of the vaccine group versus 3.2% in the placebo group reported symptoms that prevented normal everyday activities (grade 3), mostly due to solicited injection-site reactions (most often pain) and systemic reactions (myalgia - most common, fatigue and headache). After a mean follow-up of 3.5 years, the occurrence of serious adverse events, potential immune-mediated diseases, or death, were similar between the vaccine and the placebo group [116]. Cunningham et al. found comparable results (ZOE-70) [117] which were also consistent with those of other studies [121-124]. Schmader et al. concluded that although grade 3 reactogenicity occurred, the physical functioning and quality of life of older adults (aged ≥50) were not affected by a first dose of Shingrix® [125]. After a follow-up period of 6 and 9 years, no vaccine related serious adverse events were reported [119, 126].
Tricco et al. conducted a meta-analysis and concluded that Shingrix® was associated with more adverse events at injection sites than Zostavax® (relative risk 1.79; 95%CI: 1.05-2.34) and placebo (relative risk 5.63; 95%CI: 3.57-7.29) [120].
For subcutaneous administration, local reactogenicity of Shingrix® may be greater than for conventional intramuscular administration [127].

4.2.4 Immunogenicity

The vaccine has shown to be immunogenic (both humoral and cellular responses) when administered as 2 doses 2 months apart [121, 122]. An additional study showed that immune responses when the second dose was administered at 6 months were non-inferior to those when the second dose was administered at 2 months [128]. Two doses of Shingrix® induced robust humoral and cellular responses that remained above baseline 3 years after vaccination [129]. Immune responses persisted for 6 and 9 years [119, 126]; based on modelling existing data, immune responses are predicted to remain above pre-vaccination levels at 15 years [119].
Leroux-Roels et al. found that 2 doses of Shingrix® induced stronger antibody responses than 2 doses of Varilrix® (a paediatric formulation with attenuated VZV) [123]. Levin et al. showed that, compared with Zostavax®, Shingrix® generated higher gE- and VZV-specific memory Th1 responses, which may explain the sustained protection [130]. Administration of Shingrix® resulted in a substantial immune response that was comparable between subcutaneous and intramuscular administration [127].

4.2.5 Specific populations

Immunocompromised population

Shingrix® is a non-live vaccine that, in principle, may also be suitable for immunocompromised people. However, efficacy and safety in this group were not studied in the initial trial. Shingrix® was well tolerated and immunogenic in adult autologous hematopoietic stem cell transplant recipients [131], and preliminary results of another study showed a vaccine efficacy of 68.2% (95%CI: 55.6-77.5%) while no safety issues occurred [132]. The vaccine was also immunogenic and had a clinically

acceptable safety profile in HIV-infected adults until the end of the study (18 months) [133].
Clinical trials examining the safety and immunogenicity of Shingrix® in renal transplant patients, and solid organ and hematologic malignancies are ongoing [134, 135].

Adults with a prior history of HZ
Shingrix® is also immunogenic and safe in adults aged ≥50 with a prior history of HZ [136].

Adults previously vaccinated with Zostavax®
Grupping et al. studied the immunogenicity and safety of two doses of Shingrix® 2 months apart in adults aged ≥65 previously vaccinated with Zostavax® ≥5 years earlier. Cellular immunogenicity, reactogenicity, and safety were comparable between previous Zostavax® recipients and Zostavax®-naive individuals up to month 12 after the second dose, indicating that prior vaccination with Zostavax® does not negatively impact the immune responses to Shingrix® [137].

4.2.6 Combination with other vaccines

Schwarz et al. demonstrated comparable safety and immunogenicity of Shingrix® and quadrivalent inactivated influenza vaccine (IIV4) when vaccines are administered concomitantly at different sites on day zero followed by a second dose of Shingrix® at month 2, as compared to serial administration of the influenza vaccine on day zero and Shingrix® at months 2 and 4 [138]. Maréchal et al. observed no immunologic interference between Shingrix® and PPV23® when co-administered in adults aged ≥50. The immune responses to both vaccines were similar between people who received the first dose of Shingrix® at the same time as the PPV23® vaccine and those who received both vaccines consecutively. Furthermore, no safety concerns were raised [139].
Evaluation of co-administration with other vaccines such as Prevenar 13® and Boostrix® is ongoing.

4.3 International use

A full overview of worldwide recommendations regarding HZ vaccination is not available. According to the vaccine scheduler of ECDC (https://vaccine-schedule.ecdc.europa.eu/, situation at 27 June 2018) and a recent overview by Weinberger [140], vaccination against HZ is at least recommended in Austria, Czech Republic, France, Greece, Italy and the United Kingdom in the EU, and in the US.
Due to the unknown burden of HZ in most countries and insufficient data concerning the use of the relatively new HZ vaccines, WHO does not yet offer any recommendation concerning the routine use of HZ vaccine [141].

In England, the HZ vaccination programme started in September 2013. At this moment, vaccination with Zostavax® is routinely offered to immunocompetent people aged 70 and as a catch-up to people aged 78. All those eligible to receive the vaccine remain eligible until the age of 80.

In the US, HZ vaccination with Zostavax® has been recommended since 2006 for immunocompetent adults aged ≥60, by the Advisory Committee on Immunization Practices (ACIP) [142]. Recently, the Advisory Committee on Immunization Practices (ACIP) recommended that Shingrix® is preferred over Zostavax® for the prevention of HZ and related complications, that the target group be extended to all immunocompetent ≥50-year-olds, and that individuals previously vaccinated with Zostavax® should be revaccinated [143].

5 Cost-effectiveness of vaccination

Several systematic reviews have been conducted on the cost-effectiveness of HZ vaccination with one dose of Zostavax® [144-147]. Virtually all included studies concluded that HZ vaccination of individuals aged 60-75 is likely to be cost-effective if the average duration of vaccine protection is at least 10 years. The two studies specifically conducted for the Netherlands found that, from a cost-effectiveness point-of-view, the optimum age of vaccination would be 70 years; the incremental cost-effectiveness ratio (ICER) was estimated at € 21,716 and € 29,664 per quality-adjusted life year (QALY) gained using a vaccine price of € 77 and € 87 per dose, respectively [148, 149]. Comparing studies from different countries is difficult due to differences in input data, model assumptions, cost-effectiveness thresholds, and discounting rates. The majority of studies reported that the ICER was most sensitive to vaccination age, vaccine price, and duration of vaccine-induced protection [144-147].
More recent cost-effectiveness analyses not included in the systematic reviews, also concluded that HZ vaccination with Zostavax® could be a cost-effective intervention - even if recent data on the duration of protection were taken into account - [150-156], except for one study that focused on 50-year old individuals [157].

Because of the limited duration of Zostavax® protection [49], the cost-effectiveness of a booster dose after 10 years has also been investigated. Le and Rothberg found that such a booster could be cost-effective [158], and initiating HZ vaccination in individuals aged 70 with one booster dose after 10 years was estimated as the most cost-effective vaccination schedule (vaccination at age 60 plus two boosters was more effective, but had an unfavourable cost-effectiveness profile) [159].

Curran et al. and Watanabe et al. modelled the public health impact of Zostavax® and Shingrix® in the German and Japanese population. They demonstrated the superior public health impact of Shingrix® due to the higher, sustained vaccine efficacy [160, 161]. Le and Rothberg investigated the cost-effectiveness of vaccination of Shingrix® (2 doses) and Zostavax® (one dose) in the United States. They concluded that Shingrix® (with assumed efficacy duration of 18.5/19.3 years depending on age) was highly cost-effective compared to no vaccination for people aged ≥60 (ICER by vaccination age: 60 years $ 30,084 per QALY, 70 years $ 20,038 per QALY, and 80 years $ 21,726 per QALY). Furthermore, Shingrix® was more effective and less expensive than Zostavax® at all vaccination ages [162]. Curran et al. also showed that vaccination with Shingrix® is cost-effective compared to no vaccination and cost-saving compared to Zostavax® in the US population aged above 60 [163].
Van Oorschot et al. estimated the ICER for Shingrix® in the German population at € 37,000 and € 44,000 per QALY for people aged ≥60 and ≥70, respectively [164]. For Hong Kong, You et al. found ICERs between $ 46,267-$ 64,341 per QALY, depending on vaccination age [165].

In a recent Dutch cost-effectiveness analysis, de Boer et al. investigated Shingrix® (two doses) and Zostavax® (one dose, or one dose plus a booster after 10 years). Shingrix® was found to be superior in reducing the burden of HZ compared to both Zostavax® alternatives (Table 5.1), but the cost-effectiveness depended largely on vaccine price.
A two-way sensitivity analysis showed that there were vaccine price combinations of Shingrix® and Zostavax® in which either Shingrix® (two doses), Zostavax® (one dose) or Zostavax® (one dose plus booster after 10 years) could be the most cost-effective alternative (Figure 5.1).
The optimum vaccination age of Shingrix® was 60-80 years. The maximum vaccine cost per series of Shingrix® to remain cost-effective (defined as less than € 20,000 per QALY gained) ranged from € 109.09 for 70-year-olds to € 63.68 for 50-year-olds. The maximum vaccine cost per dose of Zostavax® varied considerably by age, ranging from € 51.37 per dose for 60-year-olds to € 0.73 per dose for 80-year-olds [166].
In this study, the incremental cost-effectiveness ratio (ICER) of Zostavax® was higher than in previous analyses for the Netherlands [148, 149], mainly due to a lower QALY loss per HZ case, and the exclusion of additional protection against PHN and HZ-related burden of illness. Other important differences were the inclusion of updated incidence rates using a new method and long-term follow-up data of Zostavax® efficacy. See Appendix 1 for more detailed information on differences between the three Dutch analyses.

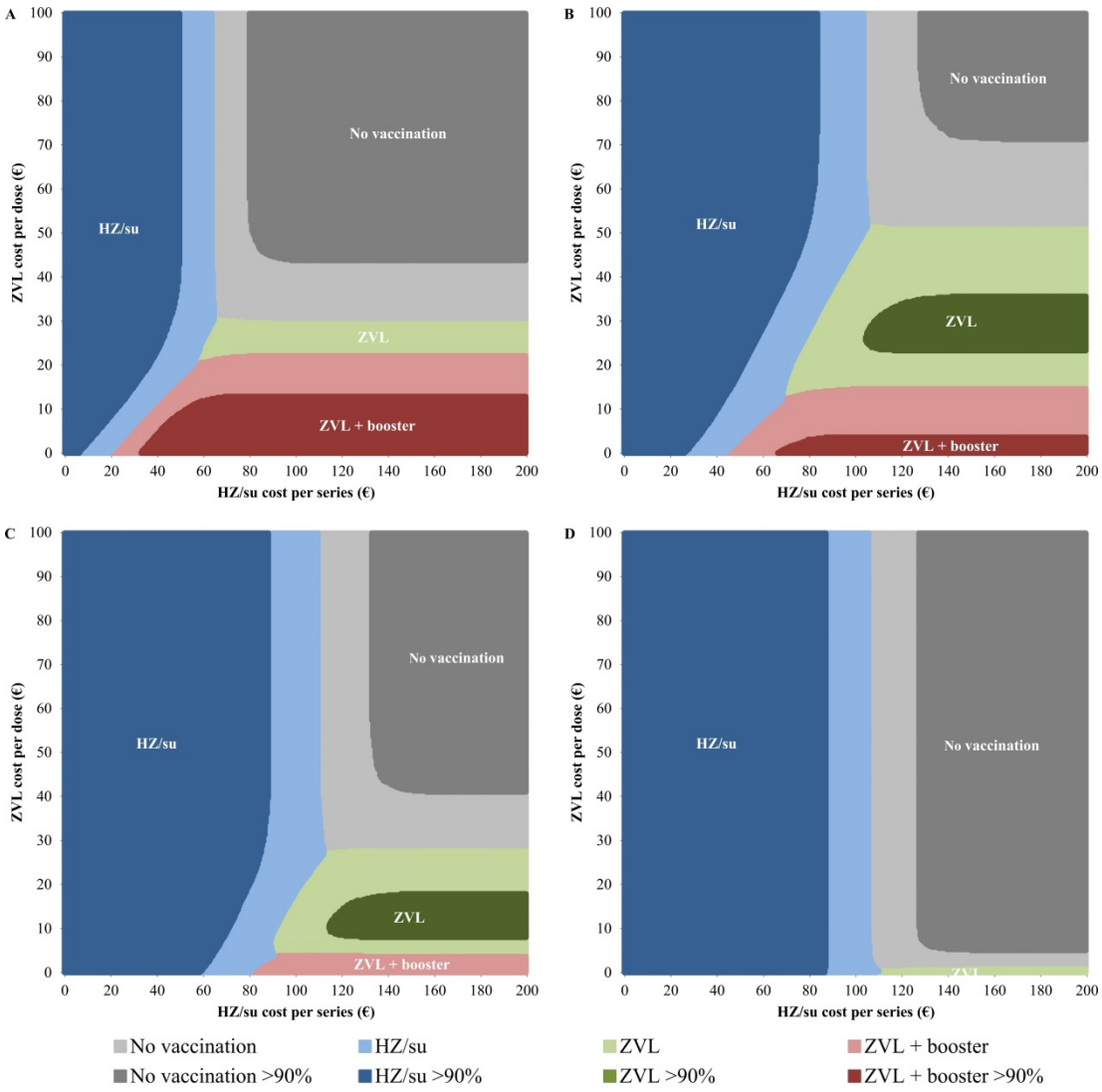

Figure 5.1 Two-way sensitivity analysis of the vaccine cost per series of Shingrix® and vaccine cost per dose of Zostavax® for vaccination of (A) 50-year-olds, (B) 60-year-olds, (C) 70-year-olds, and (D) 80-year-olds.
After performing a probabilistic sensitivity analysis using 10,000 Monte Carlo simulations, the alternative with the highest probability of being cost-effective to a willingness-to-pay threshold of € 20,000 per QALY gained is presented over a range of vaccine cost. Dark coloured areas indicate that the probability of being the most cost-effective alternative is higher than 90%.
HZ/su: Shingrix®, ZVL: Zostavax®.

Table 5.1 Impact, effectiveness and cost-effectiveness of vaccination of Dutch immunocompetent older adults against herpes zoster at a coverage of 50% over a period of 15 years. Vaccination strategies include Shingrix® (two doses) or Zostavax® (single dose, or single dose + booster after 10 years). Future costs and quality-adjusted life years (QALYs) include an annual discount rate of 4% and 1.5%, respectively.

Vaccination strategy	Total HZ cases	HZ cases averted	PHN cases averted	QALYs gained	Total costs saved (€, millions)	NNV to prevent a HZ case	Threshold vaccine cost to equal € 20,000 per QALY (€)[a]	Threshold vaccine cost to equal € 50,000 per QALY (€)[a]
50 years								
No vaccination	22,613							
Zostavax®	18,618	3,995	118	159.3	2.060	31.7	29.59	67.29
Zostavax® + booster	16,392	6,220	281	268.1	2.777	20.4	27.09	65.51
Shingrix®	14,141	8,472	324	351.6	4.026	15.0	63.68	146.91
60 years								
No vaccination	27,093							
Zostavax®	22,215	4,877	358	266.9	1.698	22.8	51.37	123.23
Zostavax® + booster	20,627	6,466	474	345.5	2.012	17.2	37.79	95.37
Shingrix®	16,833	10,260	753	548.9	3.270	10.9	104.30	252.09
70 years								
No vaccination	31,481							
Zostavax®	28,368	3,113	228	176.9	0.724	34.9	27.48	76.38
Zostavax® + booster	27,645	3,836	281	215.4	0.865	28.3	19.43	58.42
Shingrix®	20,585	10,896	799	599.9	2.400	10.0	109.09	274.91
80 years								
No vaccination	11,449							
Zostavax®	11,050	400	29	24.7	0.092	117.0	0.73	16.56
Zostavax® + booster	11,022	427	31	26.4	0.095	109.5	-1.45	11.69
Shingrix®	7,114	4,335	318	256.6	0.930	10.8	106.03	270.59

[a] Cost per series (two doses) of Shingrix® or cost per dose for Zostavax®. Administration costs of € 11.36 per dose and travel costs of € 0.43 per dose are not included. HZ: Herpes zoster, NNV: Number needed to vaccinate, PHN: Post-herpetic neuralgia, QALY: Quality-adjusted life-year.

6 Acceptance of vaccination

6.1 Acceptance of vaccination in the Netherlands

Several questionnaire studies have been conducted by the RIVM on the acceptance of new vaccinations among professionals and the public. Eilers et al. studied the vaccine preferences and acceptance of older adults and concluded that prominent factors that influence vaccination choices of older adults are: vaccine effectiveness, susceptibility for a disease, and mortality caused by a disease. They also estimated a potential vaccination rate for HZ of 58.1% (49.5% among persons aged 50-65 versus 67.5% among persons aged above 65) [167].

Many studies showed that recommendation by a physician is a crucial factor for the elderly to accept vaccination in general, or for vaccination against HZ in particular [168-174]. However, Lehmann et al. showed that the intention of Dutch general practitioners to offer vaccination against HZ to people aged above 60 was low (10.5%); in comparison: the intention to offer vaccination against pneumococcal disease was much higher (74.6%) [175].
Many older people are either institutionalised or visit other specialists besides their GP due to co-morbidity. Semi-structured interviews among eight elderly care specialists in nursing homes showed that they have little knowledge about available vaccinations and do not seem to perceive a role for them in informing the elderly about vaccination. Financial resources, additional time, and clear guidelines with a focus on the elderly were stated as prerequisites for expanding their role in vaccination care [176].

A previous study by Opstelten et al. conducted in 2007 in the Netherlands showed that the uptake of HZ vaccination (39%) was fairly low compared to the uptake of influenza vaccination (76%), when free HZ vaccination was offered simultaneously with the annual influenza vaccination. Determinants of noncompliance with HZ vaccination were again perceived lack of recommendation by the GP, but also an unwillingness to comply with the doctor’s advice, perception of low risk of contracting HZ, perception of short pain duration of HZ, and the opinion that vaccinations weaken one’s natural defences [171].

Finally, the uptake of influenza vaccination in the Netherlands among people aged above 60 shows a decreasing trend in recent years, and no longer reaches the EU target of 75% [177, 178].

6.2 Acceptance of vaccination in other countries

In England, where vaccination against HZ (with Zostavax®) was introduced in 2013, vaccination coverage was estimated at 59.5% (95%CI 59.3-59.7%) and has shown a decline over time [50, 179]. Figure 6.1 shows the most recent uptake figures [180]. Crude coverage ranged from 49.6% (95%CI: 49.0-50.2%) in London to 64.8% (95%CI: 63.9-65.7%) in South Central. Compared to the White-British group, coverage was lower in all other ethnic groups [179].

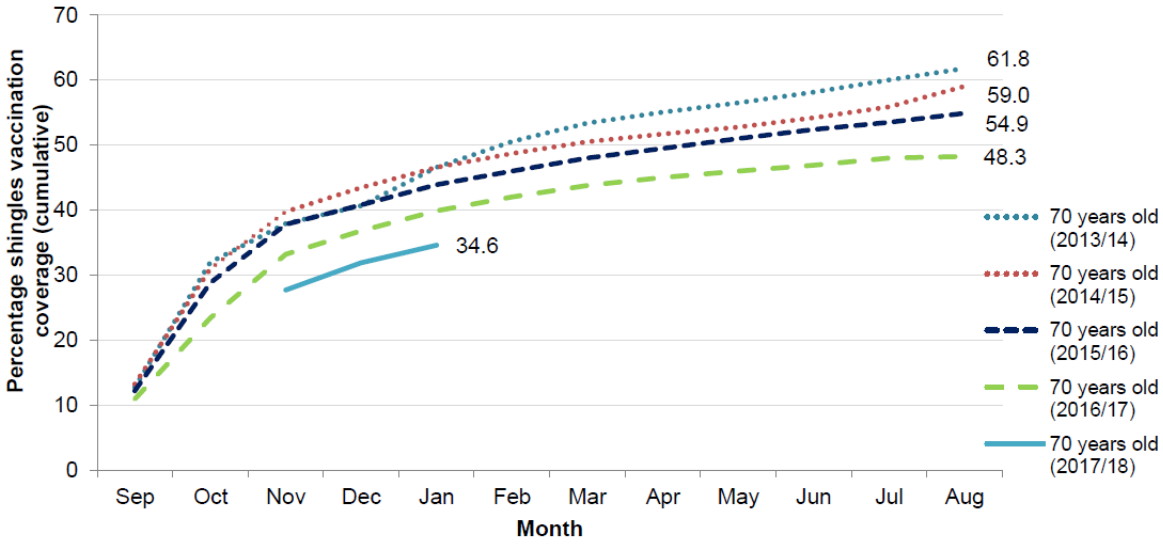

Figure 6.1 Monthly cumulative herpes zoster vaccination coverage in November 2017 to January 2018 for individuals aged 70 on 1 September 2017, compared to routine cohorts in 2016/2017, 2015/2016, 2014/2015 and 2013/2014, England [180]*

*September and October 2017 data not available

In contrast, since 2006, coverage has remained low in the US after the recommendation to vaccinate against HZ (with Zostavax®). In 2007 the coverage was estimated at 1.9% (95%CI: 1.3-2.8%) [181], in 2008 at 6.7% (95%CI: 5.9-7.6%) [182]. By 2013, vaccination coverage among adults aged ≥60 was estimated at 19.5% based on a claims database [183]. Based on the 2014 Behavioral Risk Factor Surveillance, the coverage was higher with 31.8% (95%CI 31.4-32.2%) but varied considerably by state from 17.8% (95%CI 15.8-20.0%) in Mississippi to 46.6% (95%CI 44.3-48.8%) in Vermont [184]. Substantial heterogeneity across states remained after adjusting for individual characteristics associated with vaccination [185].

To date, no results of vaccination coverage regarding Shingrix® have been published as the vaccine was only registered in 2018.

7 Aspects of implementation

The current HZ vaccines are both licensed for use in people aged above 50 in a two-dose schedule for Shingrix® (with the second dose given two to six months after the first), and as a single dose for Zostavax® with the need for a booster dose after approximately 10 years (Chapter 4).

In principle, Shingrix®, a non-live vaccine, might be suitable for immunocompromised people, however this has only been confirmed in a small number of research studies. Although Zostavax®, being a live-attenuated vaccine, is contraindicated in the immunocompromised, multiple studies showed immunogenicity and safety in different groups of immunocompromised patients (Chapter 4).

Shingrix® has a higher efficacy than Zostavax® but requires two doses and is associated with more adverse events at injection sites. Both vaccines can be administered concomitantly at different anatomic sites, with quadrivalent inactivated influenza vaccine (IIV4). Programmatic vaccination against HZ might therefore be combined with the 'Nationaal Programma Griepppreventie' in which people aged above 60 are invited for the annual flu vaccination. However, the logistics would have to account for a second dose of Shingrix® 2-6 months after the first dose, and flu vaccination is only organised once a year. Both vaccines can also be co-administered with pneumococcal vaccine (Pneumovax 23®) (Chapter 4). This might be important in the future, as the Health Council of the Netherlands recently advised offering pneumococcal vaccination to people aged 60-75, every five years, with Pneumovax 23® [186].

As with all vaccine-preventable diseases for which universal vaccination has been introduced, monitoring and active surveillance are essential. These should cover surveillance of vaccine uptake, disease surveillance (mandatory notification is currently not included in the Public Health Law), pathogen surveillance, immunosurveillance, and surveillance of adverse events. Furthermore, the duration of long-term protection of the vaccines is important. Monitoring considerations will vary according to the vaccination strategy.

Currently, hardly any HZ vaccinations are prescribed or administered in the Netherlands. Although programmatic HZ vaccination is currently not in place in the Netherlands, people can decide to get vaccinated at their own expense. For this purpose, information on HZ vaccination for professionals (factsheet) and the public (Q&A) is available on the RIVM website (developed as part of the project 'Vaccinatie op maat').

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Appendix 1 Comparison of different cost-effectiveness analyses of vaccination against herpes zoster (HZ) (and post-herpetic neuralgia (PHN)) in the Netherlands

Differences in	**De Boer et al. (2018)**	**De Boer et al. (2013)**	**Van Lier et al. (2010)**
General aspects			
Vaccines	Shingrix®, Zostavax®	Zostavax®	Zostavax®
Perspective economic evaluation	Societal perspective (indirect costs included).	Both societal (indirect costs included) and health care payer's perspective.	Societal perspective (indirect costs included).
Included ages of vaccination	50 / 60 / 70 / 80	60 / 65 / 70 / 75	60 / 65 / 70 / 75 / 80
Target population	Restricted to immunocompetent people, because efficacy trials were conducted in this group and Zostavax® is contraindicated in immunocompromised people.	Restricted to immunocompetent people because Zostavax® is contraindicated in immunocompromised people.	Assumption: 5% will not benefit from vaccination because Zostavax® is contraindicated in immunocompromised people.
Time-horizon	15 years	Life-time	Life-time
Model	Markov model with decision tree	Cohort model	Cohort model
Input parameters			
Number of doses	1) Shingrix®: 2 within 2-6 months 2) Zostavax®: 1 3) Zostavax®: 1 + booster after 10 years	1	1
Vaccine price	Threshold analysis in which the vaccine price per dose that equals € 20,000/QALY gained was estimated.	€ 87	€ 77

Differences in	De Boer et al. (2018)	De Boer et al. (2013)	Van Lier et al. (2010)
Administering costs			
- Application costs (per vaccination)	€ 11.36 (influenza tariff)	€ 4.80 (half the influenza tariff, assuming co-administration with influenza vaccine)	€ 4.80 (half the influenza tariff, assuming co-administration with influenza vaccine)
- Coordination costs (per vaccination)	-	€ 1.65	€ 1.65
- Once only costs	-	-	€ 0.3 million costs for education of GPs, developing information material (invitation letter, flyer, publicity campaign, website), adjustment of software for registration and monitoring, and administration (these costs were not included in the model).
Vaccine uptake	50%	100%	100%

Differences in	De Boer et al. (2018)	De Boer et al. (2013)	Van Lier et al. (2010)
Vaccine efficacy and duration of protection	Shingrix®: based on large trials by Lal et al. (2015) and Cunningham et al. (2016). A linear waning rate was estimated, with a duration of protection of 26 years for 50-69 years and 24 years for ≥70 years. Zostavax®: based on large trials by Oxman et al. (2005) and Schmader et al. (2012). Duration of protection was estimated using long-term efficacy data from Morrison et al. (2015). After fitting a 1-exponential model, the duration of protection ranged from 14 years for 50-69 years to 4 years for 80+ years. A booster dose was assumed to have the same efficacy as a first dose would have had at that age. Additional efficacy against PHN was restricted to the sensitivity analysis.	Estimated by Pellissier et al. (2007) based on a large trial by Oxman et al. (2005). An exponential decay of vaccine protection was assumed with a base case duration of protection of 12 years. Additional efficacy against BOI and PHN was included for ≥70 years only.	Estimated by Van Hoek et al. (2009) based on a large trial by Oxman et al. (2005). The vaccine efficacy was split into two parameters, a take (initial vaccine efficacy) and waning (reduction of protection over time) estimated on initial trial data. The base case duration of protection was only 7.5 years and was estimated to be between 3.6 to 100 years, with an age dependent take. Three different scenarios: protection against HZ, burden of illness, PHN.

Differences in	De Boer et al. (2018)	De Boer et al. (2013)	Van Lier et al. (2010)
Incidence herpes zoster	NIVEL 2012-2015 (Schurink-van 't Klooster & de Melker, 2017): incidence of GP consultations (~520 per 100,000 population per year) by age plus correction for false positives (10%: 7.9-12.4%) (Van Hoek et al., 2009). NB: due to adapted method of NIVEL, the HZ incidence is considerably higher from 2012 onwards.	NIVEL 1998-2001 (de Melker et al., 2006): incidence of GP consultations (~325 per 100,000 population per year) by age. Age specific proportions of PHN after HZ (Opstelten et al., 2002).	NIVEL 2002-2007 (Verheij et al., 2009): linear regression incidence of GP consultations (~330 per 100,000 population per year) by age plus correction for false positives (10%: 7.9-12.4%) (Van Hoek et al., 2009).
Hospitalization due to herpes zoster (main diagnosis)	National Medical Register (LMR) 2012-2014 (Schurink-van 't Klooster & de Melker, 2017): clinical hospital admissions (~380 per year) and admissions for one day (~650 per year) by age (ICD-9 code 053/ICD-10 code B02).	National Medical Register (LMR) 1998-2001 (Schurink-van 't Klooster & de Melker, 2017): clinical hospital admissions (~430 per year) by age (ICD-9 code 053).	National Medical Register (LMR) 2000-2007 (Schurink-van 't Klooster & de Melker, 2017): clinical hospital admissions (~370 per year) and admissions for one day (~1010 per year) by age (ICD-9 code 053).
Death due to herpes zoster (primary cause of death)	Statistics Netherlands (CBS) 2012-2016 (Schurink-van 't Klooster & de Melker, 2017): ~26 deaths per year (ICD-10 code B02).	Exclusion of mortality (conservative approach) as it is unknown whether it concerned immunocompromised or not).	Statistics Netherlands (CBS) 2000-2007 (Schurink-van 't Klooster & de Melker, 2017): ~18 deaths per year (ICD-10 code B02 and G530).
QALY loss	Based on Van Wijck et al. (2017). Substantial lower QALY loss than used in De Boer et al. (2013) and Van Lier et al. (2010).	Utility values (Oster et al., 2005, Bala et al., 1998, Pellissier et al., 2007) and the duration of QALY losses (Oxman et al., 2005, Gauthier et al., 2009, Moore et al., 2010) were derived from the literature.	Estimated by Van Hoek et al. (2009).

Differences in	De Boer et al. (2018)	De Boer et al. (2013)	Van Lier et al. (2010)
Costs	Presented in 2017 Euros and based on Dutch guidelines on pharmacoeconomics 2016 (National Health Care Institute, 2016).	Presented in 2010 Euros and based on Dutch guidelines on pharmacoeconomics 2010 (Hakkaart-van Roijen et al., 2010).	Presented in 2008 Euros and based on Dutch guidelines on pharmacoeconomics 2004 (Oostenbrink et al., 2004).
- Direct costs of disease	Costs for GP visits, prescribed medication, specialist visits, one-day hospital admissions, hospitalisations. Costs due to over-the-counter (OTC) medication and travelling (De Boer et al., 2018; see additional file/supplement).	Costs for GP visits, hospitalisations, drugs and pharmacy dispensing fees (De Boer et al., 2013; see Table 2).	Costs for GP consultation, use of antivirals and pain medication, hospitalisation (Van Lier et al., 2010; see additional file 2).
- Indirect costs of disease	Costs due to health-care costs in gained life years using a tool from Van Baal (2011) and productivity losses of patients aged 50-69 due to work absenteeism and presenteeism based on productivity loss from Van Wijck et al. (2017).	Updated labour participation rates from the CBS and included production losses of patients aged ≥65.	Work loss till the age of 65: an average of € 32.04 lost per day or € 324 for the total work loss for someone in the age group 60-65.
Discount rates	4% for costs and 1.5% for effects	4% for costs and 1.5% for effects	4% for costs and 1.5% for effects

Differences in	De Boer et al. (2018)	De Boer et al. (2013)	Van Lier et al. (2010)
Results			
Maximum vaccine price to remain cost-effective / most optimal ICER	The optimum vaccination age of Shingrix® was 60-80 years with a corresponding maximum vaccine cost of € 104.30-109.09 per series to remain cost-effective (less than € 20,000 per QALY gained). The maximum vaccine cost of Zostavax® varied considerably by age, ranging from € 51.37 per dose for 60-year-olds to € 0.73 per dose for 80-year-olds	€ 29,664 per QALY for vaccination of 70-year-olds.	€ 21,716 (95% CI: € 11,569 - € 31,870) per QALY for vaccination of 70-year-olds (marginal cost-effective).
Number needed to vaccinate (NNV) to prevent a herpes zoster case	For: Zostavax®, Zostavax® + booster, and Shingrix® 50 years: 31.7, 20.4, 15.0 60 years: 22.8, 17.2, 10.9 70 years: 34.9, 28.3, 10.0 80 years: 117.0, 109.5, 10.8	For: Zostavax® 60 years: 24.2 65 years: 27.5 70 years: 33.2 75 years: 48.4	For: Zostavax® 60 years: 40.6 65 years: 38.4 70 years: 49.9 75 years: 59.7 80 years: 124.7

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