Health Relevance of Shingles Vaccination in the Elderly Population

Medical Need, (Cost-)Effectiveness & Implementation

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Serial number: Report 2015-09
Date: 9 September 2015
ISBN: 978-94-91526-06-0

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The expert procedure is supported by the Foundation Ephor (expertise centre pharmacotherapy in old persons). www.ephor.nl

Information

This report has included information up till July 1st, 2015.

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For this expert procedure an unrestricted grant has been received from Sanofi Pasteur MSD.

Information

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Summary

The context of healthy aging and the need for prevention by vaccination

Due to the serious challenge of demographic aging with a doubling of the elderly population aged 65 and above by 2060, and, on top of that, the proportion of elderly suffering from chronic diseases (>70%), 'healthy aging' and 'the prevention of diseases in the elderly' are assigned to be the key priorities for most European member states, including the Netherlands. However, yet, less than 3% of the actual health budgets across Europe and also in The Netherlands is dedicated to prevention activities.

Since the immune status of the elderly population is deteriorating by natural ageing, a process called immunosenescence, and the high prevalence of chronic conditions among the elderly population puts an additional burden on their immune status, elderly have an increased susceptibility for infections. Vaccination is an effective measure for prevention against some of these infectious diseases.

Recently, the Public Health England (PHE), an autonomous executive agency of the Department of Health in the United Kingdom (UK), published the first results of the implementation of a shingles (herpes zoster, HZ) vaccination programme for the elderly population in primary care centers in the UK. We noted that The Netherlands, with its similar primary care vaccination infrastructure and its similar disease incidence and medical need among the elderly population, still awaits implementation of a HZ vaccination programme. This observation triggered us to use HZ vaccination as an example for studying the possibilities for 'healthy aging' and 'prevention of diseases in the elderly population by vaccination'.

A multidisciplinary expert committee from The Netherlands was installed to explore the background and outcomes of the UK's national HZ vaccination programme in depth, to review current European and national policies for prevention and subsequently to assess the health relevance of HZ vaccination for the elderly population in The Netherlands. Health relevance is an instrument applied to integrate both scientific evidence as well as evidence from daily practice or real life in weighing and defining the medical and societal need for a medical intervention, specifically, in the present case, HZ vaccination among the elderly population.

Herpes Zoster and postherpetic neuralgia

Herpes zoster (HZ) is a painful disease, characterized by the typical one-sided vesicular rash in one or, sometimes, a few dermatomes. It is caused by the reactivation of the varicella zoster virus (VZV), the virus causing chickenpox mainly during childhood. The incidence is highly age dependent, with a sharp increase after the age of 50 years owing to immunosenescence. In individuals >50 years of age the incidence is around 7–8/1,000 increasing to 10/1,000 in people >80 years of age. The most common and serious complication of patients with HZ is the very painful and difficult-to-treat persistent pain syndrome defined as postherpetic neuralgia (PHN). The incidence of PHN varies between 9% among HZ patients in 60-64 years of age and > 50% among HZ patients >80 years of age. PHN results in a prolonged loss of quality of life and high burden of illness. In about 16% of affected individuals PHN may last at least two years and in about 10% can persist even for four years. In the acute phase, early systemic antiviral therapy together with adequate pain therapy is the mainstay

treatment of HZ across Europe. It reduces the duration of viral shedding and lesion formation, and therefore decreases the severity and duration of acute pain from HZ. Despite antiviral and pain treatment of HZ, the complication PHN is not prevented and once established, adequate analgesic therapy is difficult and referral to a pain specialist or a pain clinic is often recommended. However, none of the analgesic therapies is sufficiently effective.

Vaccination

As neither HZ nor PHN can be sufficiently treated, vaccination is an important potential solution. In The Netherlands most vaccinations are offered through the national routine immunisation programmes (NIP). Other options are the Health Insurance Act or out-of-pocket (e.g. travelers vaccines). The NIP is extensive for children but contains only one vaccine for elderly, i.e. the influenza vaccine for people aged ≥60 or for those who are <60 years of age and have a medical indication for vaccination. The Health Council of The Netherlands (HC) states that older people will be increasingly a target for public vaccination programmes due to their aging immune system and, therefore, susceptibility to infections. The Minister of Health, Welfare and Sports (further abbreviated by Minister of Health), currently, reorganizes vaccination as an important part of a future sustainable healthcare development.

Herpes Zoster Vaccine

Since May 2006, the first live attenuated injectable herpes zoster vaccine (HZ vaccine), Zostavax, is available worldwide. HZ vaccine is indicated for prevention of HZ and HZ-related PHN in adults aged 50 years or above. Compared with placebo, a single dose of HZ vaccine reduced the incidence of HZ in those aged 50-59 years, 60 years and above and in those aged 70 years and above by 69.8%, 51.3% and 38% respectively. The incidence of PHN was reduced in those aged 60 years and over by 66.5% and 66.8% in those aged 70 years and above. The Burden of Illness (BOI) in those aged 50-59 years, 60 years and above and in those aged 70 years and above was reduced by 73%, 61.1% and 55.4% respectively. HZ vaccine has a low-risk safety profile. The most frequent adverse reactions, reported in ≥1% of participants vaccinated with HZ vaccine, were headache and injection-site reactions. The current range of cost-effectiveness ratios (~€10,000 - € 29,664 per QALY gained) is mostly influenced by duration of vaccine efficacy, vaccine price, HZ incidence and discount rates. If co-administration of HZ vaccine and influenza vaccine is integrated into the current established national influenza vaccination programme in the primary care infrastructure, this may lead to an improvement of the cost-effectiveness ratio of HZ vaccination in The Netherlands.

Recently, the results were published of a new HZ vaccine, currently under research, i.e. a recombinant subunit herpes zoster vaccine (HZ/su) containing the vaccine antigen VZV glycoprotein E, adjuvanted with $AS01_B$ which is currently not a licensed adjuvant. Two doses of HZ/su vaccine, administered 2 months apart, had a sustained vaccine efficacy of 97.2% among all age groups, as compared with placebo, in reducing the risk of herpes zoster in adults aged 50 years and above. Side effects were provoked by the reactogenicity of HZ/su vaccine (2.2 times more solicited systemic reactions than placebo).

Assessment of HZ vaccine by independent health authorities in Europe

Four independent European health authority bodies have published assessment reports on HZ vaccination. In 2013, the European Health Technology Assessment (HTA) Group ´EUnetHTA´ (a voluntarily cooperation of European Health Authorities), assessed prevention with HZ vaccine for individuals ≥50 years of age. EUnetHTA considered HZ vaccine more effective in preventing HZ than placebo with a similar safety profile as placebo. No further recommendation for implementation was provided to Ministries of Health of individual European member states. Also in 2013, the French health authorities (Haute Conseil de la Santé Publique, HCSP) assessed HZ vaccine. Based on the added value of HZ vaccine, they recommended to implement vaccination with HZ vaccine for adults aged 65 to 74 years and to perform a catch-up programme for adults aged 75 to 79 years. In June 2015, the French Ministry of Health decided to provide partial reimbursement for an individual vaccination in these age groups. In 2014, the National Health Care Institute (Dutch: Zorginstituut Nederland, ZINL) assessed a subgroup of 70-79 years of age. ZINL considered therapeutic added value of HZ vaccine in the prevention of HZ and PHN in immunocompetent adults of 70 years or above. Despite a recommendation for implementation, a decision by the Ministry of Health is still pending.

In 2010, the UK's Joint Committee on Vaccination and Immunisation (JCVI) recommended that a national HZ vaccination programme with HZ vaccine should be introduced for adults aged 70 years with a catch-up programme for those aged 70 to 79 years. Instead of an individual programme, such as that in the United States (US), where coverage is 20.1% of adults aged ≥60 years (first year coverage 1.9%), the JCVI chose for a national vaccination programme because of the significant increased risk of developing the disease and the significant increased burden of disease in elderly aged ≥70 years resulting more frequently in complications such as PHN and an increase in hospital admissions, justifying the avoidance of health inequalities among individuals. Furthermore, the JCVI considered prevention of the disease burden most cost-effective for those aged 70 to 79 years.

Introduction, implementation and outcomes a national HZ vaccination programme in the UK

The programme was implemented in 2013 by PHE. For monitoring coverage and the impact of the programme on the incidence of HZ and PHN, PHE has established a number of surveillance systems across primary care centres and pain clinics. In December 2014, the first year outcomes of the implementation of the HZ vaccination programme with HZ vaccine were published by PHE: 'Herpes zoster (shingles) immunization programme 2013/2014: Report for England'. PHE highlights the successful implementation of the first year of the HZ vaccine programme in the UK, given the vaccine coverage of almost 62% for the routine cohort (age 70 years), and almost 60% for the catch-up cohort (age 79 years).

Assessment of the health relevance of HZ vaccination for The Netherlands;
a comparison between the UK and The Netherlands

For the assessment of the medical need of HZ vaccination for the elderly population, we align with the conclusions of independent bodies like the JCVI in the UK and the HC and ZINL in The Netherlands. Departing from established guidelines indicating that despite antiviral and pain treatment of HZ, PHN is not prevented and knowing that vaccination with HZ vaccine reduces

clinically relevant the incidence of the most common and most severe complication of HZ, i.e. PHN, with 67% in the population of 70 years and above, we endorse the medical need for a HZ vaccine in the national immunisation programme for the elderly population in The Netherlands.
It has been highlighted by the PHE in the UK that the national HZ vaccination programme has achieved a high vaccine coverage in the first year of almost 62% for the routine cohort, and almost 60% for the catch-up cohort. The initial high HZ vaccine coverage is due to the nation-wide execution alongside the existing national seasonal influenza vaccination programme and due to the well-established primary care infrastructure in the UK. The coverage within an individual programme is usually considerably lower, as is demonstrated in the United States (US) with a coverage of 20.1% of adults aged ≥60 years and above (in the first year of the programme, 2007, coverage was 1.9%). High coverage is required from a health care perspective, given the undisputed medical need, therefore justifying the avoidance of health inequalities among individuals. Therefore, we conclude that the availability of an established primary care infrastructure and the possibility of co-administration of both influenza and HZ vaccines, provides the 'high way' to high coverage of HZ vaccination.
Due to the serious challenge of demographic aging with a doubling of the elderly population aged 65 and above by 2060, healthy aging and prevention are assigned to be the key priorities for most European member states, including the Netherlands. Knowing the effects of immunosenescence and knowing that the high prevalence of chronic conditions among the elderly population puts an additional burden on the immune system, timely vaccination is an effective way to establish protective immunity. Although other preventive programmes, like cervical and colon cancer screening, may be more cost-effective (€9,000, respectively <€20,000 per QALY (Quality-adjusted Life Year)), the cost-effectiveness of the HZ vaccination programme compares well to the recently introduced HPV vaccination programme for 12-year old-girls (€18,400 - €30,000 per QALY) as well to the influenza vaccination programme (>€20,000 per QALY). We conclude that the current evidence of vaccine effectiveness and safety, the cost-effectiveness outcomes and the 10 years of real-life experience with the HZ vaccine, combined with the positive outcomes of the national HZ vaccination programme in the UK, justifies uptake of HZ vaccination in the national vaccination programme for elderly populations in The Netherlands. Based on analytical studies showing that the most cost-effective age for offering the vaccination to prevent HZ and/or to reduce the disease burden is for those aged 70 to 79, we suggest to align with the UK vaccination programme and to routinely offer the HZ vaccine to adults aged 70 years and to adults aged 71-79 as part of a gradual catch-up programme. The comparability between the primary-care infrastructure of the UK and that of The Netherlands, makes it highly likely that the outcomes of the implementation of a national HZ vaccination programme within the primary-care infrastructure may also be as successful for The Netherlands. It is also expected that more efficiency can be reached by running two vaccination programmes alongside each other, providing also a better cost-effectiveness for both influenza and HZ vaccination programmes.

Recommendation
Based on strong clinical rationales (the undisputed medical need and therefore the justification for avoidance of health inequality) and societal rationales (demographic challenges, prevalence of co-

morbidity, immunosenescence, healthy aging and vaccination as effective measure for prevention, as well as the comparability of the HZ vaccine and influenza vaccine in effectiveness, safety and cost-effectiveness), we acknowledge the 'health relevance' of uptake of the HZ vaccine in the national vaccination programme for the elderly population. The already 10 years of worldwide experience with HZ vaccination and the successful example of the UK's HZ vaccination programme, further strengthen our suggestion to the Minister of Health, Welfare and Sports, to align with the UK vaccination programme by extending the Dutch national influenza vaccination programme for the elderly population with HZ vaccination for adults aged 70 years, with a gradual catch-up programme for those aged 71 to 79 years. Compared to influenza vaccine, the HZ vaccine needs to be administered only once and has a duration of efficacy of at least 7-10 years. Whereas co-administration of HZ vaccine and influenza vaccine is feasible, this may provide an opportunity from an organizational as well as from a cost-effective point of view to vaccinate with HZ vaccine and influenza vaccine simultaneously.

Samenvatting

Gezond ouder worden en de noodzaak van ziektepreventie door vaccinatie

Vanwege de verdubbeling van de bevolking van 65 jaar en ouder in 2060, en het aandeel van ouderen die lijden aan chronische ziekten (>70%), zijn 'gezond ouder worden' en 'preventie van ziekten bij ouderen' belangrijke prioriteiten voor de meeste Europese lidstaten. Dit blijkt evenwel niet uit de cijfers: minder dan 3% van het gezondheidszorgbudget in Europa en ook in Nederland wordt besteed aan preventie.

Door de afname van de functie van het afweersysteem bij ouderen als gevolg van veroudering, de zogenaamde “immunosenescence’, en de hoge prevalentie van chronische ziekten bij ouderen, schiet het afweersysteem van ouderen tekort met als gevolg een verhoogde vatbaarheid voor infecties. Vaccinatie is een effectieve preventieve maatregel voor een aantal veel voorkomende bacteriële of virale infecties.

Onlangs, heeft het agentschap van het ministerie van Volksgezondheid in het Verenigd Koninkrijk (VK), de ‘Public Health England’ (PHE), de eerste resultaten gepubliceerd van het landelijke Herpes Zoster (HZ) ofwel gordelroos vaccinatieprogramma in de huisartsenpraktijk. Ondanks de vergelijkbare huisartsenzorg, vergelijkbare ziekte-incidentie en medische behoefte onder ouderen is zo’n vaccinatie programma in Nederland (nog) niet beschikbaar. Deze observatie was aanleiding om HZ vaccinatie als voorbeeld te gebruiken voor het bestuderen van de mogelijkheden voor 'gezond ouder worden' en 'preventie van ziekten bij ouderen door middel van vaccinatie’.

Een multidisciplinaire commissie van deskundigen uit Nederland werd gevormd, om de achterliggende beweegredenen en de resultaten van het Engelse nationale HZ vaccinatieprogramma te bestuderen. Voorts werd het huidige Europese en nationale beleid voor preventie bestudeerd, om vervolgens de ‘gezondheidsrelevantie’ van HZ vaccinatie van ouderen in Nederland te beoordelen. Gezondheidsrelevantie is een instrument dat beoogd om zowel wetenschappelijk bewijs als ervaring vanuit de dagelijkse praktijk te integreren bij de beoordeling van de medische en maatschappelijke noodzaak voor een medische interventie, in dit geval, HZ vaccinatie van ouderen

Herpes zoster en postherpetische neuralgie

Herpes zoster (HZ) of gordelroos is een pijnlijke aandoening, gekenmerkt door typische eenzijdige blaasjes-achtige huiduitslag in één of soms meerdere dermatomen. Het wordt veroorzaakt door de reactivering van het varicella zoster virus (VZV), het virus dat waterpokken veroorzaakt met name gedurende de kinderleeftijd. De incidentie is in hoge mate afhankelijk van de leeftijd, met een scherpe toename na de leeftijd van 50 jaar als gevolg van immunosenescence. In volwassenen >50 jaar is de incidentie ongeveer 7-8/1.000 toenemend tot 10/1.000 bij volwassenen >80 jaar. De meest voorkomende en meest ernstige complicatie van patiënten met HZ is de zeer pijnlijke en moeilijk te behandelen postherpetische neuralgie (PHN). De incidentie van PHN varieert tussen 9% bij HZ patiënten van 60-64 jaar en >50% bij HZ patiënten >80 jaar. PHN resulteert in een langdurig verlies van kwaliteit van leven en een hoge ziektelast. In ongeveer 16% van de getroffen individuen houdt PHN ten minste twee jaar aan en bij ongeveer 10% kan het zelfs vier jaar aanhouden. In de acute fase is vroege systemische antivirale therapie gecombineerd met adequate pijnbestrijding de

standaardbehandeling van HZ in heel Europa. Deze behandeling vermindert de duur van virale blaasjes vorming en verspreiding van het virus, en vermindert daardoor de ernst en duur van de acute pijn door HZ. Ondanks antivirale en pijnbehandeling van HZ, wordt de complicatie PHN niet voorkomen en wanneer PHN eenmaal is vastgesteld, is adequate pijnbestrijding moeilijk en is doorverwijzing naar een pijnspecialist of een pijnkliniek vaak nodig. Naar de huidige stand van wetenschap zijn geen van de pijnbehandelingen voldoende effectief.

Vaccinatie

Aangezien noch HZ noch PHN afdoende behandeld kan worden, is vaccinatie een belangrijke oplossing om ziektelast te voorkomen of te verminderen. In Nederland worden de meeste vaccinaties aangeboden via het Rijksvaccinatieprogramma (RVP). Andere opties zijn via de Zorgverzekeringswet of uit eigen middelen (bijvoorbeeld reizigersvaccins). Het RVP omvat een uitgebreid programma voor kinderen, maar bevat slechts één vaccinatie voor ouderen, de influenza (griep) vaccinatie voor ouderen ≥60 jaar of voor degenen <60 jaar met een medische indicatie voor vaccinatie. De Gezondheidsraad (GR) stelt dat ouderen toenemend een doelgroep vormen voor publieke vaccinatieprogramma's als gevolg van hun ouder wordende afweersysteem en dientengevolge hun vatbaarheid voor infecties. De minister van Volksgezondheid, Welzijn en Sport (VWS) reorganiseert op dit moment de vaccinatiezorg als een belangrijk onderdeel van een toekomst bestendige duurzame gezondheidszorg.

Herpes zoster vaccin

Sinds mei 2006, is het eerste levende verzwakte injecteerbare herpes zoster vaccin (HZ-vaccin, merknaam Zostavax) wereldwijd beschikbaar. HZ vaccin is geïndiceerd voor de preventie van HZ en-HZ-gerelateerde PHN bij personen van 50 jaar of ouder. In vergelijking met placebo, verminderde een enkele dosis van het HZ vaccin de incidentie van HZ met 69.8%, 51,3% en 38% in respectievelijk de leeftijdsgroepen 50-59 jaar, 60 jaar en ouder en 70 jaar en ouder. De incidentie van PHN werd in de leeftijdsgroep van 60 jaar en ouder met 66,5% vermindert en met 66,8% in de leeftijdsgroep van 70 jaar en ouder. De ziektelast in de leeftijdsgroep van 50-59 jaar, 60 jaar en ouder en 70 jaar en ouder, werd verminderd met respectievelijk 73%, 61.1% en 55.4%. HZ vaccin werd goed verdragen. De meest voorkomende bijwerkingen bij ≥1% van de deelnemers, die werden gevaccineerd met het HZ-vaccin, waren hoofdpijn en lokale irritatie op de injectieplaats. De range in kosteneffectiviteit ratio's (~ €10.000 - €29.664 per QALY) wordt vooral beïnvloed door de duur van de werkzaamheid van het vaccin, de HZ incidentie en de prijs van het vaccin. Indien de eenmalige HZ-vaccinatie organisatorisch geïntegreerd wordt met de influenza vaccinatie binnen het RVP, kan dit in Nederland leiden tot een verdere verbetering van de kosten-effectiviteitsratio van HZ vaccinatie.

Onlangs werden de resultaten gepubliceerd van een nieuw HZ vaccin, dat nog in onderzoek is. Het is een recombinant subunit herpes zoster vaccin (HZ/su) met het vaccin-antigen VZV-glycoproteïne E en het, ongeregistreerde, adjuvans AS01B. Twee doses van HZ/su vaccin, toegediend om de 2 maanden, bij volwassenen van 50 jaar en ouder liet in alle leeftijdsgroepen een reductie van het risico op HZ met 97,2% zien in vergelijking met placebo. De vaccinatie met het HZ/su vaccin leidde tot 2,2 keer meer systemische reacties dan placebo.

Beoordeling van het HZ vaccin door onafhankelijke gezondheidsautoriteiten in Europa
Vier onafhankelijke Europese gezondheidsautoriteiten hebben beoordelingsrapporten met betrekking tot HZ vaccinatie gepubliceerd. In 2013, beoordeelde de 'European Health Technology Assessment' (HTA) Groep 'EUnetHTA' (een vrijwillig samenwerkingsverband van Europese gezondheidszorgautoriteiten), de preventie met het HZ vaccin voor individuen ≥50 jaar.[15] EUnetHTA oordeelde dat het HZ vaccin effectiever was in het voorkómen van HZ dan placebo, met een vergelijkbaar veiligheidsprofiel als placebo.[15] Er werd geen verdere aanbevelingen voor de implementatie van het vaccin gegeven aan de ministeries van Volksgezondheid van de individuele Europese lidstaten. Eveneens in 2013, evalueerde de Franse gezondheidsautoriteit (Haute Conseil de la Santé Publique, HCSP) het HZ vaccin. Op basis van de toegevoegde waarde van het HZ vaccin, werd geadviseerd om vaccinatie met het HZ vaccin te implementeren bij volwassenen van 65-74 jaar met een inhaal programma voor volwassenen van 75-79 jaar. In juni 2015 heeft het Franse ministerie van Volksgezondheid besloten om de individuele vaccinatie bij genoemde leeftijdsgroepen gedeeltelijk te vergoeden. In 2014 heeft het Zorginstituut Nederland (ZINL) de toepassing van het HZ vaccin voor een subgroep van 70-79 jarigen beoordeeld. ZINL stelde een therapeutische meerwaarde vast voor het HZ vaccin bij de preventie van HZ en PHN bij immuuncompetente volwassenen van 70 jaar of ouder. Ondanks een aanbeveling voor implementatie van het vaccin, heeft de Minister nog geen besluit genomen. In 2010, heeft de Britse 'Joint Committee on Vaccination and Immunisation' (JCVI) geadviseerd om een nationale HZ vaccinatieprogramma met het HZ vaccin te implementeren voor volwassenen van 70 jaar met een inhaal programma voor de leeftijdsgroep van 70-79 jaar. In plaats van een individueel programma, zoals dat in de Verenigde Staten (VS) wordt gevolgd, waarbij de vaccinatiegraad van volwassenen ≥60 jaar circa 20,1% bedraagt (vaccinatiegraad in het eerste jaar 1,9%), heeft de JCVI gekozen voor een nationaal vaccinatieprogramma. De belangrijkste beweegredenen voor de rechtvaardiging van een landelijke implementatie en daardoor het vermijden van ongelijke toegang tot zorg, waren het significant verhoogd risico op het ontwikkelen van de ziekte en de aanzienlijke ziektelast bij ouderen ≥70 jaar, bij wie frequenter complicaties optreden, zoals PHN en een toename van het aantal ziekenhuisopnames. Bovendien, oordeelde de JCVI dat preventie van HZ en PHN het meest kosteneffectief is in de leeftijdsgroep 70-79.

Introductie, implementatie en uitkomsten van het Engelse nationale HZ vaccinatieprogramma
Het Engelse nationale HZ vaccinatie programma werd in 2013 geïmplementeerd onder leiding van PHE. Voor de monitoring van de vaccinatiegraad en de impact van het programma op de incidentie van gordelroos en PHN, heeft PHE een aantal surveillance systemen opgezet onder de huisartsenpraktijken en pijncentra. In december 2014 werden door PHE de eerstejaars resultaten van het HZ vaccinatieprogramma gepubliceerd: "Herpes zoster (shingles) immunisation programme 2013/2014: Report for England'. PHE wijst op de succesvolle uitvoering van het eerste jaar van het programma, gezien de vaccinatiegraad van bijna 62% voor het cohort van 70 jaar, en bijna 60% voor het inhaal-cohort van 79 jaar.

Beoordeling van de gezondheidsrelevantie van HZ vaccinatie voor Nederland; een vergelijking tussen het Verenigd Koninkrijk en Nederland
Voor de beoordeling van de medische noodzaak van HZ vaccinatie bij ouderen, sluiten wij aan bij de

conclusies van de onafhankelijke instanties zoals de JCVI in het VK en de GR en ZINL in Nederland. Uitgaande van bestaande richtlijnen waaruit blijkt dat ondanks de antivirale en pijnbehandeling van HZ, PHN niet wordt voorkómen en uitgaande van een klinisch relevante afname van de incidentie met 67% van de meest voorkomende en meest ernstige complicatie van HZ, i.e. PHN, door vaccinatie met het HZ vaccin van ouderen van 70 jaar en ouder, onderschrijven wij de medische noodzaak van opname van het HZ vaccin in het Rijksvaccinatieprogramma voor ouderen in Nederland.
De PHE in het VK rapporteerde dat het nationale HZ vaccinatieprogramma in het eerste jaar een hoge vaccinatiegraad heeft behaald van bijna 62% voor het 70-jarige cohort en bijna 60% voor het inhaal-cohort van 79-jarigen. Dit is enerzijds door de landelijke uitvoering van het programma, dat naast het bestaande nationale influenzavaccinatie programma wordt uitgevoerd en anderzijds dankzij de goed georganiseerde infrastructuur van de huisartsenpraktijken in het VK. De vaccinatiegraad bij een individueel vaccinatie programma is aanzienlijk lager, zoals blijkt uit het individueel HZ vaccinatie programma in de VS met 20,1% bij volwassenen ≥60 jaar (in het eerste jaar van het programma, 2007, was de vaccinatiegraad 1,9 %). Gegeven de onbetwiste medische noodzaak, is een hoge dekkingsgraad zinvol vanuit gezondheidszorgperspectief. Daarbij is ongelijke toegang tot zorg tussen individuen daarmee te vermijden. Wij concluderen daarom dat de goede infrastructuur van huisartsenpraktijken in Nederland en de mogelijkheid om gelijktijdig het influenza en het HZ vaccin toe te dienen, de beste manier is om een hoge vaccinatiegraad van HZ vaccinatie te bereiken.
Hoewel andere preventieve programma's, zoals baarmoederhalskanker en darmkanker screening, kosten-effectiever zijn (€9.000, respectievelijk <€20.000 per QALY), is de kosten-effectiviteit van een HZ vaccinatieprogramma vergelijkbaar met de onlangs geïntroduceerde HPV vaccinatie voor 12-jarige meisjes (€18.400 - €30.000 per QALY), alsook met het influenza vaccinatie programma (>€20.000 per QALY). We concluderen dat de huidige gegevens met betrekking tot de effectiviteit en veiligheid van het HZ vaccin, de kosten-effectiviteitratio en de 10 jaar praktijkervaring met het HZ vaccin, in combinatie met de positieve resultaten van het nationale HZ vaccinatieprogramma in het VK, de opname van HZ vaccinatie in het RVP voor ouderen in Nederland rechtvaardigt.
Gebaseerd op studies waaruit blijkt dat de meest kosteneffectieve leeftijd voor het aanbieden van de vaccinatie om HZ te voorkomen en/of om de ziektelast te verminderen, de leeftijdsgroep 70-79 jarigen is, adviseren we de minister van VWS om het Engelse vaccinatieprogramma te volgen en HZ vaccinatie routinematig aan te bieden aan volwassenen van 70 jaar, evenals aan volwassenen van 71-79 jaar als onderdeel van een geleidelijk inhaal programma. De vergelijkbaarheid tussen de huisartsenzorg van het VK en die van Nederland, doet vermoeden dat de uitvoering van een nationaal HZ vaccinatieprogramma in de huisartsenpraktijken net zo succesvol zal verlopen voor Nederland. Tevens wordt verwacht dat meer efficiëntie kan worden bereikt door het uitvoeren van twee vaccinatieprogramma's naast elkaar, waardoor ook een betere kosten-effectiviteit voor zowel het influenza als het HZ vaccinatieprogramma ontstaat.

Aanbeveling

Op basis van klinische en maatschappelijke beweegredenen bevestigen wij de 'gezondheidsrelevantie' van de opname van het HZ-vaccin in het RVP voor ouderen in Nederland. De al 10 jaar wereldwijde praktijkervaring met HZ vaccinatie en het succesvolle voorbeeld van het

Engelse HZ vaccinatie programma, versterkt onze aanbeveling aan de minister van VWS, om, naar analogie van het Engelse vaccinatieprogramma, het RVP voor ouderen uit te breiden met HZ vaccinatie voor volwassenen van 70 jaar met een geleidelijk inhaal programma voor de leeftijdsgroep 71-79 jaar. Vergeleken met het influenza vaccin, wordt het HZ vaccin maar eenmalig toegediend en heeft het een werkingsduur van tenminste 7-10 jaar. Door de mogelijkheid van gelijktijdige toediening van het HZ-vaccin en het influenza vaccin, kan vanuit organisatorisch oogpunt als ook vanuit kosten-effectiviteit oogpunt het HZ vaccinatie programma parallel lopen binnen de huidige structuur van het nationale influenza vaccinatie programma.

Abbreviations

ACIP	Advisory Committee on Immunization Practices
ADL	Activities of Daily Living
AIDS	Acquired Immune Deficiency Syndrome
AIRDs	Autoimmune inflammatory rheumatic diseases
ASIA	Autoimmune/inflammatory Syndrome Induced by Adjuvants
AT	Area team
BKV	Beoordelings Kamer Vaccins
BOI	Burden of illness
BPS	British Pain Society
CBS	Statistics Netherlands (Dutch: Centraal Bureau voor de Statistiek)
CCGs	Clinical commissioning groups
CD4	Cluster of differentiation 4
CI	Confidence Interval
CIb	Centre for Infectious Disease Control
CPRD	Clinical Practice Research Datalink
CVZ	College voor Zorgverzekeringen; currently National Health Care Institute (ZINL)
EMA	European Medicine Agency
EU	European Union
EULAR	European league against rheumatism
EUnetHTA	European HTA Group
ESWI	European Scientific Working group on Influenza
FAcadMed	Fellow Academy of Medical Educators
FBGTHA	Fellow British Global & Travel Health Association
FESC	Fellow European Society of Cardiology
FFTM RCPS	Fellow Faculty of Travel Medicine, Royal College of Physicians & Surgeons
FRCGP	Fellow Royal College of General Practitioners
g	gram
GDP	Gross Domestic Product
GP	General Practitioner
GR	Gezondheidsraad
HC	Health Council of The Netherlands
HCSP	Haute Conseil de la Santé Publique
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HRQOL	Health related quality of life
HTA	Health Technology Assessment
HZ	Herpes zoster
HZO	Herpes zoster ophthalmicus
HZ/su	Recombinant subunit herpes zoster vaccine
ICERs	Incremental cost-effectiveness ratios
ICPC	International Classification of Primary Care
IgG/IgA	Immunoglobulin G/ immunoglobulin A
I&M	Ministry of Infrastructure and Environment
i.m.	Intramuscular
JCVI	Joint Committee on Vaccination and Immunisation
kg	kilogram
LINH	National Primary care practice Information Network (Dutch: Landelijk Informatie Netwerk Huisartspraktijken)

MA	Marketing Authorisation
mg	milligram
MMR	Measles, Mumps and Rubella
NACI	National Advisory Committee on Immunization
NHG	English: Dutch College of General Practitioners (Dutch: Nederlands Huisartsen Genootschap)
NHS	National Health Service
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research (Dutch: Nederlands Instituut voor onderzoek van de Gezondheidszorg)
NL	The Netherlands
NNT	Number-needed-to-treat
NNTB	Number needed to treat to benefit
NPP	National Prevention Programme
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVI	Netherlands Vaccine institute
PCRN	Primary Care Research Network
PFU	Plaque forming units
PHE	Public Health England
PHN	Post herpetic neuralgia
PPV	Pneumococcal polysaccharide vaccine
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RCGP	Royal College of General Practitioners
RCT	Randomised controlled trial
RIVM	English: National Institute of Public Health and the Environment (Dutch: Rijksinstituut voor Volksgezondheid en Milieu)
SLE	Systemic Lupus Erythematosus
SPS	Shingles Prevention Study
SSRIs	Selective Serotonin Reuptake Inhibitors
SWZ	English: Ministry of Social Affairs and Employment (Dutch: Ministerie van Sociale Zaken en Werkgelegenheid)
TB	Tuberculosis
TCAs	Tricyclic Antidepressants
TNF	Tumour Necrosis Factor
UK	United Kingdom
US	United States of America
VE	Vaccine effectiveness
VAS	Visual Analogue Scale
VK	Verenigd Koninkrijk
vs.	versus
VS	Verenigde Staten
VTV	The Future Health Report (Dutch: Volksgezondheid Toekomst Verkenning)
VWS	Ministry of Health (Dutch: Ministerie van Volksgezondheid, Welzijn en Sport)
VZV	Varicella zoster virus
Wbo	Law for Population Screening (Dutch: Wet op het bevolkingsonderzoek)
Wpg	Public Health Act (Dutch: Wet publieke gezondheid)
ZEST	Zostavax Efficacy and Safety Trial
ZINL	National Health Care Institute (Dutch: Zorginstituut Nederland)
ZQOL	Zostavax Quality of Life Study
Zvw	Health Insurance Act (Dutch: Zorgverzekeringswet)

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1.1 Introduction

1.1.1 Rationale of this report

Within the European Union (EU), including the Netherlands, there is considerable interest in the relationship between 'healthy aging' and prevention of diseases in the elderly population by vaccination. Recently, Public Health England, an autonomous executive agency of the Department of Health in the United Kingdom (UK), extended the long-standing influenza vaccination programme for elderly populations in primary care centers in the UK successfully with shingles vaccination. In The Netherlands, the structure of the national vaccination programme in primary care centers is comparable to that in the UK. Within Europe, both countries are well-known for their successful coverage and implementation of national vaccination programmes. The similar demographics, disease prevalence and incidence and medical need among elderly populations in both countries are also comparable, triggered us to review the Dutch situation with respect to vaccination as a measure for 'healthy aging' and 'prevention of diseases in elderly populations' in general, with shingles as an example. A multidisciplinary expert committee from The Netherlands was installed to explore the background and outcomes of the UK's national shingles vaccination programme in depth, to review current European and national policies for prevention and subsequently to assess the health relevance of shingles vaccination for the elderly population in The Netherlands. Health relevance is an instrument in which both scientific evidence as well as evidence from daily practice or real life is integrated to weigh and define the medical and societal need for a medical intervention, in the present case shingles vaccination among the elderly population.

1.1.2 Structure of the report

In part 1 we present a framework by elaborating on the actual European and national concept of 'healthy aging', and related to this, the 'need for prevention in the elderly population by interventions like vaccination'. Also the disease herpes zoster and its treatment and prevention are covered in part 1. These introductory sections are concise. More background information can be found in the addenda to this report. Part 2 of this report covers the main subject of the report. In this part, we present the assessment of the health relevance of shingles vaccination for the elderly population in The Netherlands, preceded by an introductory review of the UK shingles vaccination programme for elderly.

1.2 Introduction to the need for prevention in elderly populations

1.2.1 Demographic challenge in the European Union and The Netherlands

Though the overall size of the European population is projected to be only slightly larger in 50 years' time[1], Europe is facing a doubling of the number of people aged 65 and above from 87 million in 2010 to 148 million in 2060.[2] The proportion of the population aged 65 and above will rise from 18% to 30% and that of aged 80 and above will rise from 5% to 12% in 2060. In The Netherlands, a similar development is anticipated. The fraction of the population aged 65 and above is expected to rise from 17.8% (3,005,744) to 26% (4,692,778).[3]

1.2.2 Immunosenescence

Immunosenescence[4] [5] refers to the gradual deterioration of the immune system brought on by natural age advancement. It is considered a major contributory factor to the increased frequency of morbidity and mortality among the elderly.

1.2.3 Chronic diseases and comorbidity

Besides demographic aging, also the number of elderly suffering from a chronic disease or multi-morbidity adds to this challenge. Chronic diseases occur at all ages, but especially among the elderly. In The Netherlands among people aged 65 and above, 70% have a chronic illness.[6] In people aged 75 and above, this percentage is 79%. Of people aged 75 and above half has more than one chronic disease, 63% had two or more chronic diseases, and 32% three or more. People with a chronic disease have a poorer quality of life than healthy individuals. The rates for chronic diseases and comorbidity in the whole of Europe are more or less comparable, though slightly higher.

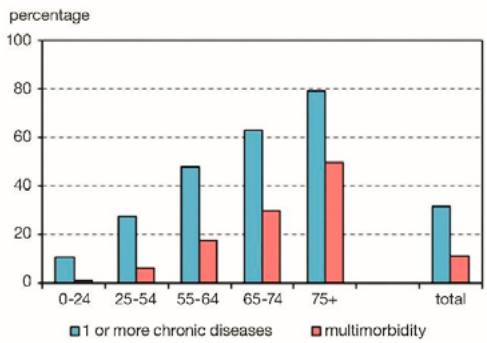


Figure 1: Percentage of people with a chronic disease and multimorbidity by age categories.[6]

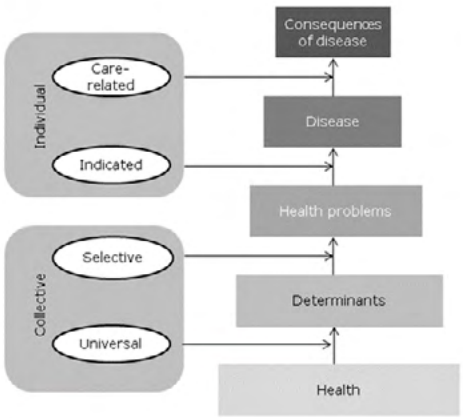
1.2.4 Political agenda on healthy aging

The European Committee and the individual EU member states are highly concerned about managing the health care issues for the elderly population.[7] [8] If this demographic transition is not tackled head-on, it will raise considerable problems in relation to the financial sustainability of health care systems. The European Innovation Partnership on Active and Healthy Ageing has been selected by the European Commission to tackle the challenges presented by an aging population. This partnership has set a target of increasing the average healthy lifespan of EU citizens by 2 years by 2020. The health and quality of life of older people focuses on actions developed around 3 pillars: (i) prevention, screening and early diagnosis; (ii) care and cure; and (iii) active aging and independent living. At the end of 2013 the Ministry of Health in The Netherlands presented in a joint action with five other ministries, the National Prevention Programme 2014-2016 (NPP)[9] to the Dutch parliament. A more prominent place for prevention in healthcare is one of the primary goals of the NPP. Furthermore, the first 6 month of 2016, VWS will fulfil the role of Chairman of the EU. One of the goals in the Dutch programme of VWS is to diminish the use of antimicrobial medicinal products within the EU.[10] Vaccination, obviously, may be a useful strategy to reach this goal.[11]

1.2.5 Prevention

Although prevention has been proclaimed as the key priority for most national health systems in the EU, yet, less than 3% of the actual health budgets across Europe is dedicated to promotion and prevention activities.[2] This is particularly important in the context of demographic change and the attention for primary prevention through targeting the key health determinants of chronic diseases. Despite the positive development away from vertical disease-specific programmes towards an integrated approach to chronic diseases and despite the strong evidence on the efficacy and cost-effectiveness of prevention, the major problem remains the unbalanced nature of health spending in both the entire EU and The Netherlands (e.g. 3% of total health care spending of 83.4 billion in The Netherlands in 2012[12]). Thus, there is an urgent need for policy change. In The Netherlands, prevention is regulated by law. The Public Health Act (Dutch: Wet publieke gezondheid, Wpg) and the Law on Population Screening (Dutch: Wet op het bevolkingsonderzoek, Wbo) represent the main legal framework to protect and promote the health of the population. Prevention is classified in four categories (figure 2). According to the national Health Care Institute (Dutch: Zorginstituut Nederland, ZINL) universal and selective prevention are collective forms of prevention (the focus being on the population) and need to be paid by the municipal or national government. By contrast, indicated and care-related prevention aim at individuals rather than the population, and fall therefore under the Health Insurance Act.

Figure 2: Dutch classifications of prevention.[12]



1.3 Introduction to vaccination for elderly populations

1.3.1 Structure of vaccination care in The Netherlands

In The Netherlands, vaccination practice is organized through a public programme (National Immunisation Programme, NIP; Dutch: Rijksvaccinatieprogramma, RVP), a health insurance programme (Health Insurance Act; Dutch: Zorgverzekeringswet, Zvw) and a free programme (table 1).[13] The Ministry of Health, Welfare and Sports (Dutch: Ministerie van Volksgezondheid, Welzijn en Sport, VWS) takes, in contrast to what is customary in the regular health care, an active and leading role.

In The Netherlands most vaccinations are offered through the NIP for children. In addition to the NIP for children a national influenza vaccination programme is in place for people ≥60 years of age or for those who are under 60 years of age and have a medical indication for influenza vaccination. The Health Council (HC), an independent scientific advisory body, advises the government and parliament on issues in the area of public health. The HC uses an assessment framework of seven criteria to support decision-making and prioritisation for the provision of a given form of vaccination for a given group.

Table 1: Overview structure, financing and implementation structure of vaccination.[13]

	Public Programme (NIP, RVP)	Health Insurance Act (Zvw)	Free market
Decision for admission	Ministry of Health (VWS)	Ministry of Health (VWS)	Ministry of Health (VWS)
Advisory Body	HC	ZINL	ZINL
Financing structure	Special budget of the Ministry of Health	Collective budget health insurers	Out of pocket
Type of care	Prevention	Indicated Care	Prevention
Implementation	Special public institutes or GP practice	In general GP practice	Special private organisations

Another system, through which vaccines may become available is the Health Insurance Act, a basic health insurance. As gatekeeper for the Health Insurance Package, ZINL plays an advisory role in this regard and has developed an own assessment framework of elements such as the effectiveness and efficiency of vaccination and also elements as necessity and feasibility. For care funded by the Health Insurance Act, the principle applies that the insured individual must be indicated for the care. In its report 'Insured for prevention' (Dutch: 'Van preventie verzekerd', 2007), ZINL speaks of *indicated*

prevention.[14] Among indicated prevention is the care that aims to prevent the occurrence of disease in an individual with an increased risk for that disease. This means that the care that aims to prevent the occurrence of disease in an individual is only indicated when this individual has a verifiable, increased risk for that disease. The basic package currently contains only a limited number of vaccines, mainly for risk groups. In this case, the primary responsibility to decide whether or not to approach the (family) doctor for vaccination rests upon the individual. Besides the above two options, there are vaccines that are available on the free market, such as travellers vaccines, which have to be paid 'out of pocket'. These vaccines are usually only given on request of the vaccinee.

1.3.2 Status of vaccination in The Netherlands

Since 1957, Dutch children have been vaccinated against infectious disease through the NIP[15], usually at clinics for infants and toddlers. The target diseases of the NIP are primarily diseases that arise in children and particularly in this subgroup can lead to serious illnesses. The NIP makes a very considerable contribution to the prevention of death and disease among children. In addition to the NIP for children, there is a national influenza vaccination programme in place for people ≥60 years of age or for those who are under 60 years of age and have a medical indication for influenza vaccination. Although the national influenza vaccination programme is not organised through the NIP, but through primary care centres, the objectives of both programmes are similar.

1.3.3 Signalling current challenges

The HC, individual vaccination experts and the Ministry of Health recently reported current challenges for the vaccination care.

Health Council (HC):[15] [16] In relation to the constant development of new vaccines, the vaccination care models and national vaccination programmes were reviewed and signals and suggestions were provided by the HC to the Ministry of Health. According to the HC it seemed probable that the NIP will increasingly become a programme for all age groups and that at the same time more possibilities will be created for vaccination outside the public vaccination programs for example via the Health Insurance Act as the place to give individuals access to preventive interventions that are considered essential care, but which serve no clear public interest. Though the Minister of Health decides about the admission of vaccines in both the NIP and in the Health Insurance Act, the different advisory bodies, i.e. HC and ZINL, assess the vaccines based on partly, different assessment criteria. This has the risk that both advisory bodies may reject an effective and efficient vaccine because it does not fit within their respective assessment frameworks. For this reason, the HC advocates for a more comprehensive advisory procedure for the entire spectrum of vaccination, illustrated by seven recommendations (see addendum, section B.3) with respect to adjusting the current structure for vaccination in The Netherlands.

Individual vaccination experts:[17] presented two additional basic ethical principles that explain why certain vaccinations are the state's moral-political responsibility, and that may further guide decision-making about the content and character of immunisation programmes. Their first principle

states that the state is responsible for protecting the basic conditions for public health and societal life. The spread of infectious diseases can have severe effects on communal life and protection against such infections is necessary for a flourishing society. This is most clear in case of a large outbreak of a dangerous disease like e.g. measles. In many cases, collective vaccination will offer such protection most effectively.
The second consideration guiding governments' responsibility for public health is justice. States are responsible for promoting and securing equal access to basic health care, which may also include certain vaccinations. In order to promote fair equality of opportunity, the state should create equal access to vaccinations that are necessary for individual persons or subgroups to maintain health. If persons or subgroups of a population run a substantial risk to develop a serious disease, and vaccination can take away or significantly reduce that risk, it might be unfair if some can afford vaccination and others cannot. If so, the government has a moral obligation to offer equal access to vaccination.

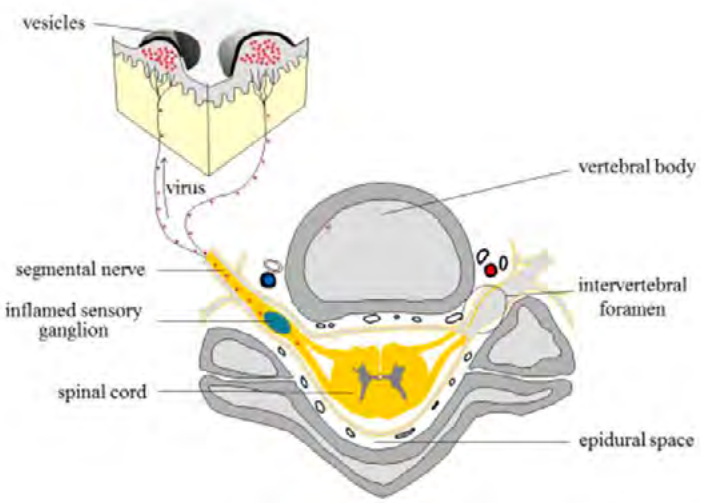
The Ministry of Health:[13] In anticipation of solving problems within the current structure (of two bodies advising on vaccination) and in anticipation of the arrival of new vaccines, the Ministry of Health has proposed a new vaccination-care model aiming to integrate procedures and advices by both the HC and ZINL about all new vaccines and aiming at formation of a Review Chamber Vaccines (Dutch: Beoordelings Kamer Vaccins, BKV) as formal partnership between the two bodies. It is intended that this collaboration will result in recommendations for narrowly defined individuals or groups for which the vaccination would be (cost-) effective and efficient and advice about the positioning of specific vaccination within the health system. In May 2015, a pilot for this new procedure has started.

1.4 Introduction to 'herpes zoster vaccination'

1.4.1 Herpes zoster, disease, incidence and complications[18 19]

Herpes zoster (HZ) is a disease among elderly caused by the reactivation of the varicella zoster virus (VZV), the virus that causes chickenpox usually during childhood. After recovery from chickenpox, the virus can remain dormant in sensory ganglia (figure 3[20]). Herpes zoster (HZ) is a painful disease, characterized by the typical one-sided vesicular rash in one or, sometimes, a few dermatomes.

Figure 3: Schematic representation of the position of the sensory ganglion in the spinal column and the transportation of the virus via the segmental nerve (drawn by G.J. Groen and A.J.M. van Wijck).[20]



The incidence is highly age dependent, with a sharp increase after 50 years. In individuals >50 years of age the incidence is around 7–8/1,000 increasing to 10/1,000 in persons >80 years of age. When shingles occurs in the area of the nervus nasociliaris, which includes not only the tip of the nose, but also the side of the nose and the medial corner of the eye, this is called herpes zoster ophthalmicus (HZO). HZO incidence ranges from 9-16% of all HZ cases, and as for HZ incidence, it increases with age.[21]

Besides age, the risk of HZ increases significantly in presence of chronic and immune-mediated diseases like autoimmune inflammatory rheumatic diseases (AIRD).[22] Impaired or premature 'ageing' of the immune system in patients with immune-mediated diseases might be responsible for deterioration of important immune functions, and therefore for a reduced protection against infections.
The most common complication of HZ is the very painful postherpetic neuralgia (PHN). Like the risk of HZ, that of PHN also increases with age. Despite early administration of anti-viral therapy, the incidence of PHN among patients suffering from HZ varies between 9% in people 60-64 years of age to over 50% in people >80 years of age.[23] PHN results in a prolonged loss of quality of life and high burden of disease.[24] In about 16% of affected individuals PHN may last at least two years and in about 10% even four years or longer.[20]

1.4.2 Treatment

Among immunocompetent patients younger than 50 years, HZ is a self-limiting disease with low risk of complications. However, for older patients, patients with impaired immunity or patients with HZ in the face, antiviral therapy may be indicated. International (Dworkin et l., 2007)[21] and national guidelines (Dutch College of General Practitioners, Dutch abbreviation NHG)[25] [26]concluded that the preponderance of findings from clinical trials provides support for the use of antiviral therapy, acyclovir, famciclovir and valacyclovir, during the acute phase, preferably <72 hours after onset of HZ to reduce acute pain and accelerate rash healing. With respect to PHN, antiviral therapy is said to have an effect on the duration of PHN, but there is no supporting evidence for an effect on the incidence of PHN. Both guidelines recommend the use of antiviral therapy only in elderly patients with serious initial symptoms and in patients with HZO. For immunosuppressed patients, hospitalization with intravenous antiviral therapy is recommended to prevent viral dissemination. In the Dutch general practice, antiviral therapy is only prescribed in 22.5% of HZ patients.
For the management of acute pain in HZ [26] paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are indicated. Only in severe pain, other treatments such as opioids, tricyclic antidepressants, anti-epileptics or epidural injections are indicated. The treatment of PHN, however, once established may be difficult and results may be disappointing. In The Netherlands antidepressants (such as nortriptyline, SSRIs, duloxetine), anti-epileptic's (including carbamazepine, phenytoin, gabapentin, pregabalin), opioids and capsaicin cream are recommended. These medicinal products have been shown to be only effective in a limited number of patients with PHN (NNT of anti-epileptics, anti-depressants and opioids varies between 2-6[27]). For patients with pain that is inadequately controlled, referral to a pain specialist or pain centre is recommended. Given the side-effects of these medicinal products, the possible interactions with other products and the low effectiveness in many patients, combined with the high impact on quality of life of the unremitting pain, a need for preventive measures is clear.

In conclusion: Despite antiviral and pain treatment of HZ, PHN is not prevented. Once established, PHN is a persistent and difficult-to-treat pain syndrome with a significant burden in terms of pain severity and deficits in health related quality of life which may persist for years.

1.4.3 Prevention

Many therapies for prevention of PHN in patients in the acute phase of HZ have been studied. Antivirals[28], corticosteroids[29], opioids, anti-epileptics and epidural injections[30] cannot prevent PHN. One small pilot-study with amitriptyline showed promising results in reducing PHN[31], but this observation needs to be confirmed. However, amitriptyline is not recommended as an appropriate therapy for elderly due to the anticholinergic side-effects.[32] As neither HZ nor PHN can be prevented by any available medical-pharmaceutical therapy, vaccination seems an important potential solution.

Herpes Zoster Vaccine[18 19 33 34 35 36 37]

Since May 2006, the first live attenuated injectable herpes zoster vaccine (HZ vaccine), Zostavax, is available worldwide.[33 83] HZ vaccine is indicated for prevention of HZ and HZ-related PHN in adults aged 50 years or above. It is contraindicated in immunocompromised patients, patients on immunosuppressive therapy and pregnant women. In two clinical studies[34 36], compared with placebo, a single dose of HZ vaccine reduced the incidence of HZ in those aged 50-59 years by 69.8%, in those aged 60 years and above by 51.3% and in those aged 70 years and above by 38%. The incidence of PHN was only measured in those aged 60 years and above and 70 years and above and was reduced by 66.5% and 66.8% respectively. The burden of illness (BOI) in those aged 50-59 years, 60 years and above and in those aged 70 years and above was reduced by 73%, 61.1% and 55.4% respectively. Effects on mortality, hospitalisation rate, health related quality of life (HRQOL), activities of daily living and pain reduction are less clear, based on methodological limitations of the studies. The probability of developing serious side effects is not significantly different between those who have been immunized with the HZ vaccine compared to placebo.

Outcomes of assessments of HZ vaccine by health authorities

In Europe, assessment reports of HZ vaccine have been published by four independent health authority bodies in Europe.[18 19 38 39] EUnetHTA considered HZ vaccine more effective in preventing HZ than placebo with a similar safety profile as placebo. No further recommendation for implementation was provided to the ministries of health in Europe. In 2010, the UK's Joint Committee on Vaccination and Immunisation (JCVI)[38] considered HZ vaccine effective in lowering the incidence and the severity of HZ in older people and recommended the Department of Health that a HZ (shingles) vaccination programme should be introduced for adults aged 70 years with a catch-up programme for those aged 70 to 79 years. This recommendation was implemented in 2013. In 2013, the European HTA Group ´EUnetHTA´ (a voluntarily cooperation of European health authorities), assessed the prevention of shingles by vaccination with HZ vaccine for individuals ≥50 years of age.[18] Also in 2013, the French health authorities ('Haute Conseil de la Santé Publique, HCSP) assessed HZ vaccine and recommended to implement vaccination with HZ vaccine for adults aged 65 to 74 years and to perform a catch-up programme for adults aged 75 to 79 years. However, it took until recently, June 2015, before the French Ministry of Health decided to provide reimbursement, in this case for an individual vaccination programme.[40] In 2014, the National Health Care Institute (Dutch: Zorginstituut Nederland, ZINL) assessed a subgroup of 70 to 79 years of age.[19] ZINL considered therapeutic added value of HZ vaccine in the prevention of HZ and PHN in immunocompetent adults. Despite a recommendation for implementation, the Ministry of Health in The Netherlands has not decided up till now (July 2015).

New development

In May 2015, phase 3 study results were published of a new HZ vaccine, i.e. a recombinant subunit herpes zoster vaccine (HZ/su, GlaxoSmithKline Biologicals) containing the vaccine antigen VZV glycoprotein E, adjuvanted with $AS01_B$ which is currently not a licensed adjuvant.[41 42] The preliminary efficacy and safety results of this new vaccine are discussed briefly in comparison to the HZ vaccine that is available since 2006.

Table 2: Comparison of HZ vaccine with HZ/su vaccine.

	HZ vaccine (Zostavax)[18 19 33 34 35 36]	**HZ/su vaccine**[41 42]
Marketing Authorisation (MA)	May 2006	No MA, currently under research
Type of vaccine	Live attenuated vaccine containing VZV	Recombinant subunit vaccine: HZ/su vaccine containing a single VZV glycoprotein in an $AS01_B$ adjuvant system
Indication	Prevention of HZ and HZ-related PHN of people aged 50 years and above	Not known yet.
Contraindications	Hypersensitivity, Primary/acquired immunodeficiency state, Under immunosuppressive therapy (exceptions topical or inhaled or low-dose systemic corticosteroids or corticosteroids as replacement therapy), Pregnancy	Not defined yet
Administration	A single dose parenteral intramuscular (i.m.) injection	A double dose, two months apart parenteral i.m. injection
Co-administration with influenza vaccine	Possible	Unknown
Co-administration with pneumococcal vaccine	Possible	Unknown
Study population	Immunocompetent population 38,546 aged ≥60 years 22,439 aged 50-59 years	Immunocompetent population 15,411 ≥50 years
Efficacy: **Prevention of HZ**	50-59 years: 69.8% ≥60 years and above 51.3% ≥70 years and above 38%	50-59 years 96.6% 60-69 years 97.4% ≥70 years and above 97.9%
Efficacy: **Prevention of PHN**	50-59 years: not measured ≥60 years and above 66.5% ≥70 years and above 66.8%	50-59 years not measured 60-69 years not measured ≥70 years and above not measured
Mortality	Comparable to placebo	Comparable to placebo
Total study population **Serious adverse events** **Substudy** **-Adverse events** **-Solicited systemic adverse events** **-Injection site reactions** **-Serious adverse events**	Measured after 42 days post-vaccination Comparable to placebo (1.4% vs. 1.4%) Adverse events substudy: 5 days post-vaccination 58% vs. 34% 25% vs. 24% 48% vs. 17% ≥60 years and above: 1.93% vs 1.29; p=0.038 ≥70 years and above: 1.66% vs 1.78%; p=0.55	Measured after 30 days Comparable to placebo (1.1% vs 1.3%) Reactogenicity study; 7 days post-vaccination 84% vs. 38% 66% vs. 30% 82% versus 12% Not reported Not reported

The recombinant subunit vaccine, currently under research, seems promising because of the sustained high efficacy among all age groups and its supposed suitability for immunosuppressed individuals.[43] Side effects were in particular provoked by the reactogenicity of HZ/su vaccine (2.2 times more solicited systemic reactions than placebo), whereas in the HZ vaccine (live attenuated vaccine) study the rates of systemic adverse events were similar compared to placebo.[42] Previous studies suggest that the antigen and the adjuvant both contribute to the difference in solicited injection-site and systemic reactions.[44] The benefits from inclusion of an adjuvant incorporation in any vaccine formulation have to be balanced against the risk of adverse reactions. Exacerbation or triggering of immune-mediated diseases in susceptible persons is a hypothetical concern for vaccines containing new adjuvants such as $AS01_B$ because of their immunostimulatory effects. Adjuvants have recently been implicated in the new syndrome named 'ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants', which describes an umbrella of clinical conditions including post-vaccination adverse reactions.[45] The administration of two doses, two months, apart may risk non-compliance, and thereby reduced health gain. Further, it involves another visit to medical centres for the second dose of the vaccine.

1.4.4 Cost-effectiveness of prevention

Cost-effectiveness of shingles vaccination: Numerous cost-effectiveness evaluations have been carried out internationally, which have been evaluated in a recent review (De Boer et al., 2014).[46] Three other cost-effectiveness evaluations have been performed for The Netherlands by the National Institute of Public Health and the Environment (Dutch: Rijksinstituut voor Volksgezondheid en Milieu, RIVM) (Van Lier et al., 2010)[47], the University of Groningen (De Boer et al., 2013)[48] and ZINL (2014)[19]. ZINL reported a cost-effectiveness analysis from a societal perspective based on an individual vaccination approach (2014).[19] The incremental cost-effectiveness ratio (ICER) for the total population of 70-79 years of age was found to be €26,844 per QALY gained. The RIVM performed a cost-effectiveness analysis from a societal perspective based on a national (public) vaccination model (2010 and concluded that the cost-effectiveness ratio for HZ vaccination in The Netherlands is optimal for 70-year olds (€21,716 per QALY gained).[47] If additional reduction of PHN was included, the cost-effectiveness ratio improved (~€10,000 per QALY gained) but uncertainty for this scenario is high. In 2013, the University of Groningen determined the ICER of vaccination in an age- and gender-stratified cohort model for immunocompetent elderly aged 60-75 years.[48] Again, the vaccination age with the most favourable ICER was 70 years, the estimated ICER being €29,664 per QALY gained. Although in The Netherlands, there is no formally defined cost-effectiveness ratio for medical interventions, the current socially accepted threshold is €20,000 per QALY gained. The current range of cost-effectiveness ratios for HZ vaccination in different evaluations (~€10,000 - €29,664 per QALY gained) is mostly influenced by vaccine-induced protection, vaccine price and HZ incidence.
Comparison with cost-effectiveness of other prevention programmes: The RIVM integrates the cost-effectiveness evaluation of preventive programmes in The Netherlands as part of its four-yearly report about the health status of the population in The Netherlands (Future Health Report; Dutch: Volksgezondheid Toekomst Verkenning, VTV) to the Ministry of Health.[49] The reported cost-effectiveness ratios for several prevention programmes are compared in table 3. Although other preventive programmes, like cervical and colon cancer screening, may be more cost-effective

(€9,000, respectively <€20,000 per QALY gained)[49], the cost-effectiveness of the shingles vaccination programme compares well to the recently introduced HPV vaccination programme for 12-year old-girls (€18,400 - €30,000 per QALY gained) as well to the influenza vaccination programme (>€20,000 per QALY gained)[50].

Table 3: Cost-effectiveness ratios for prevention programmes in The Netherlands.

Prevention programme	Cost-effectiveness (costs per QALY gained)	Remarks
HPV vaccination in 12-year old girls[49]	€18,400 - €30,000	If a booster vaccination would be required, the cost-effectiveness ratio would increase with €5,000 per QALY.
Meningococcal catch-up of children aged 1-18 years[49]	€13,200-€17,000	A single catch-up campaign
Influenza vaccination of elderly aged ≥60 years[50]	>€20,000	The initial cost-effectiveness in 2007 was €15,500. Currently, the HC estimates >€20,000 (still to be calculated)
Pneumococcal vaccination of children aged >5 years[49]	€113,891 (PCV-7) € 52,947 (PCV-10) € 50,042 (PCV-13)	In case of dose-reduction: €113,891 (PCV-7) In case of dose-reduction: € 37,891 (PCV-10) In case of dose-reduction: € 35,743 (PCV-13)
Breast cancer screening (every two years) of women aged 50-70 years[49]	< €2,000-€5,000	
Colon cancer screening of elderly aged 50-70 years[49]	<€20,000	
Cervical carcinoma screening (every 5 years) of women aged 30-50 years[49]	€9,000	This represents the adjusted campaign; the cost-effectiveness of the initial campaign was €15,500

Part 2: Implementation of herpes zoster vaccination in the elderly population

2.1 Implementation of herpes zoster vaccination 'next door'

2.2 The comparison between the United Kingdom and The Netherlands

2.1 Implementation of herpes zoster vaccination 'next door'

2.1.1 The shingles vaccination programme in the United Kingdom

The UK is one of the few countries who introduced a national shingles vaccination programme for older adults. In 2010, the UK's Joint Committee on Vaccination and Immunisation (JCVI) recommended that a shingles (herpes zoster, HZ) vaccination programme should be introduced for adults aged 70 years with a catch-up programme over the years for those aged 70 to 79 years, with the aim to lower the incidence and severity of shingles in older people.[38 51] This recommendation was based on the review of medical, epidemiological, and economic evidence of the first available HZ vaccine, Zostavax, as well as its safety and efficacy data relevant to a HZ vaccination programme, provided that a licensed vaccine is available at a cost effective price. JCVI considered the impact of vaccination greatest (greatest benefit) in this age group 'adults aged 70 years with a catch-up programme for those aged 70 to 79 years' due to a combination of factors, including:

- an increase in the burden of shingles disease with age,
- a decrease in the effectiveness of the vaccine with age,
- the duration of protection of the vaccine, and
- the lack of knowledge about the effectiveness of a second dose of vaccine.

Figure 4: The epidemiology of shingles in England and Wales.[23]

Estimated annual age-specific incidence, hospitalisation rate, length of inpatient stay, Burden of disease in the immunocompetent population England and Wales

Age Group	Incidence per 100,000 per year (general)	Percentage developing post herpetic neuralgia after 90 days	Proportion hospitalised first diagnosis (first three diagnosis)	Mean number of days in hospital (median)
60-64	706	9%	0.8% (1.3%)	9 (4)
65-69	791	11%	1.0% (1.7%)	8 (5)
70-74	876	15%	1.5% (2.4%)	11 (5)
75-79	961	20%	2.2% (3.8%)	14 (7)
80-84	1046	27%	3.0% (5.2%)	17 (9)
85+	1216	52%	4.4% (8.1%)	22 (13)

Figure 5: The epidemiology of shingles in England and Wales.[23]

Public Health England (PHE), an operationally autonomous executive agency of the Department of Health, has issued the 'Service specification number 14; shingles immunisation programme'[52] to be exercised by the National Health Service (NHS) England. At the same time the national 'Green Book', the reference book that keeps health professionals and immunisation practitioners up to date with respect to developments and the latest information on vaccines and vaccination procedures, for vaccine-preventable infectious diseases, has been updated with the shingles vaccination programme, chapter 28.[53] [54]

Figure 6: The Green Book[53]

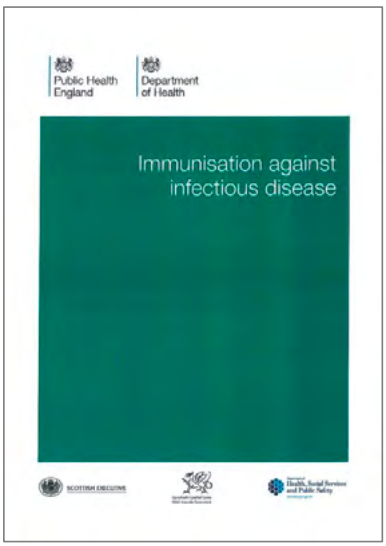


Figure 7: Shingles programme, chapter 28 of the Green Book.[54]


28a

Shingles (herpes zoster)

The disease

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In the first year of the programme (2013/14), the vaccine was routinely offered to adults aged 70 years on 1 September 2013 (the target group) and to adults aged 79 on 1 September 2013 as part of the catch-up campaign. From 1 September 2014, the programme was slightly adjusted. The immunisation is now offered to patients aged 70 for the routine programme, and not only to those aged 79 but also to those aged 78 for the catch-up programme.[55]

2.1.2 The implementation of a national shingles vaccination programme

PHE has established several surveillance systems for the monitoring of the implementation as well as the monitoring of the impact and effectiveness of the shingles vaccination programme, since its introduction on the 1 September 2013. In December 2014, PHE published the report 'Herpes zoster (shingles) immunisation programme 2013/2014: Report for England', on the evaluation of the implementation and outcomes of the first year of the HZ vaccination programme in England.[56]

Implementation of the national shingles vaccination programme[56]

In the first year of the programme (2013/14), the vaccine was routinely offered to adults aged 70 years on 1 September 2013 (i.e. born between 2 September 1942 and 1 September 1943) and to adults aged 79 on 1 September 2013 (i.e. born between 2 September 1933 and 1 September 1934) as part of the catch-up campaign. The shingles vaccination programme is from an organizational perspective, mainly executed alongside the existing influenza and pneumococcal vaccination programme for elderly aged ≥65 years and its infrastructure in the primary care. The vaccines are given simultaneously if appropriate. The Green Book[53] contains recommendations about the administration as well as implementation and monitoring system of the shingles vaccination programme. The shingles vaccination programme runs between September and the following August.

Recommendations for administration of simultaneous vaccines[56]

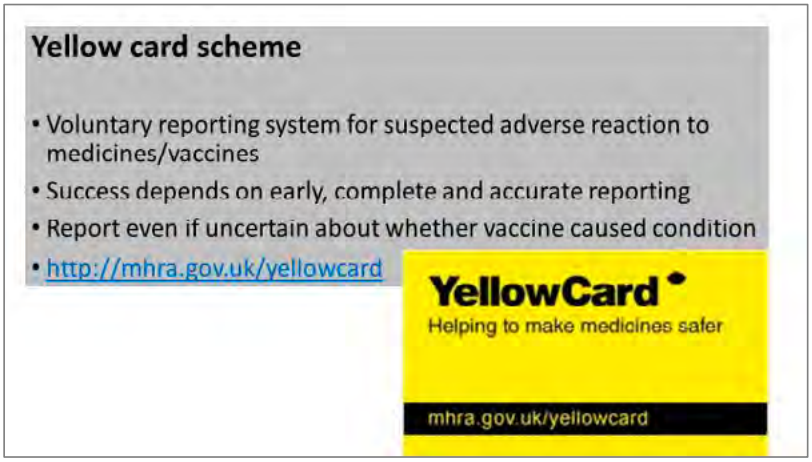
Specific recommendations for administration of simultaneous vaccines are:

- HZ vaccine is safe to be administered concomitantly with both inactivated vaccines such as influenza and 23-valent pneumococcal polysaccharide vaccine (PPV)
- MMR vaccine can lead to an attenuation of the varicella vaccine response. This may also be the case for yellow fever vaccine, but there are no data. A four-week interval is recommended between shingles vaccination and these two live vaccines.

Monitoring: surveillance systems[56]

For the monitoring of the vaccination programme, PHE has established a number of surveillance systems which include a new vaccine coverage collection via web-forms (ImmForm), which is automatically uploaded by aggregated GP practices on a monthly and annual basis. Based on regular data extraction from Clinical Practice Research Datalink (CPRD), the impact of the programme on the incidence of shingles and PHN can be monitored. The ImmForm also provides the programme for ordering vaccines from the NHS. Adverse events reporting is organized through the common Yellow card scheme.[57]

Figure 8: Yellow card scheme for reporting suspected adverse reactions.[57]



In order to supplement the proposed monitoring of PHN via CPRD, PHE, with the support of the British Pain Society (BPS) has set up a surveillance network across 74 pain clinics and 37 clinical commissioning groups (CCGs; CCGs are clinically led groups that include all of the GP practices in their geographical area)

PHE also commissioned a coding system[58] for clinical risk groups in whom shingles vaccination may be contraindicated are reported within the surveillance system. A detailed guidance is made available for interpretation of contraindications and precautions in order to individually assess whether or not a person with a listed clinical risk on her/his medical record (as defined by the coding system) should receive the shingles vaccine.[54]
In some instances these patients are also at particular risk of severe shingles disease and the clinician may decide that the vaccine would be beneficial. It is also possible that although a patient may have a relevant code in their record, the condition that this refers to may have subsequently resolved. Similarly, the patient could at one time have been on a drug that would place her/him in a risk group, but even though this may no longer be the case the medical record may not have been updated to reflect this.

Detailed guidance on contraindications and special considerations[54]

- Confirmed anaphylactic reaction to a previous dose of the vaccine or of the varicella vaccine
- Confirmed anaphylactic reaction to any of the components of the vaccine, including neomycin or gelatine
- Active untreated tuberculosis
- If individual acutely unwell – postpone vaccination (so as not to confuse signs of an acute illness with adverse effects of vaccine)

- Primary or acquired immunodeficiency state due to conditions such as:
    - Is acute and chronic leukaemia's; lymphoma; other conditions affecting the bone marrow or lymphatic system;
    - immunosuppression due to HIV/AIDS (a CD4 count of ≥200 cells/µl may be a suitable cut off point – consult hospital physician)
    - cellular immune deficiencies
- Is currently receiving immunosuppressive therapy such as:
    - Chemotherapy or radiotherapy for malignancy - do not vaccinate until 6 months after the end of treatment and with the patient in remission (discuss with oncologist)
    - High-dose corticosteroids (40 mg Prednisolone per day for more than a week) - do not vaccinate until 3 months after the end of treatment. For cohorts in the national vaccination programme (70-79 years) extend this period to 6 months
    - Biological therapies (e.g. monoclonal TNF alfa inhibitors)

  Therapy with a single, low-dose, non-biological oral immunomodulating medicinal product, either alone or with low dose steroids, are not necessarily sufficiently immunosuppressive to contraindicate administration of zoster vaccine. In these individuals, the degree of immunosuppression should be assessed on a case by case basis. Specialists with responsibility for patients in the vaccine eligible age cohorts should include a statement of their opinion on the patient's suitability for vaccination in their correspondence with primary care. If clinicians administering the vaccine have concerns about the nature of therapies (including biologics) or degree of immunosuppression they should contact the relevant specialist.
  Administration is possible in case of: methotrexate <0.4 mg/kg/week, azathioprine <3.0 mg/kg/day, 6 mercaptopurine <1.5 mg/kg/day.

- The vaccine is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids and in people who are receiving corticosteroids as replacement therapy (e.g. for adrenal insufficiency)
- Pregnancy
- Oral or intravenous antivirals (such as acyclovir) 48 hours after cessation of treatment may potential lower effectiveness of the vaccine (therapy may reduce response to vaccine)
- Disease that might lead to immunodeficiency or anticipating start of immunosuppressive therapy; vaccinate at least 14 days before (best allow a month)
- Asplenia/splenectomy is not of itself a contraindication, though the underlying cause may be (such as leukaemia or lymphoma infiltration).
- Humoral deficiencies affecting IgG or IgA antibodies are not of themselves a contraindication unless associated with T cell deficiencies. If there is any doubt (e.g. common variable immune deficiency), immunological advice should be sought.

Detailed guidance on precautions[54]

- Not recommended for the treatment of Shingles or PHN;
- In immunocompetent individuals who develop shingles, delay vaccination for a year;

- Transmission of the vaccine virus is possible and rare. If a post-vaccination vesicular rash appears, keep the rash area covered when in contact with a susceptible (varicella-naive) person until the rash is dry & crusted.
- Previous HZ infection – vaccinate but allow at least a year after the infection

Communication campaign[55]

The implementation of the vaccination programme was supported by a communication campaign. After clinicians identified patients via searches on their national computer systems. Yellow flags were put for opportunistic vaccinations to remind the GP while seeing patients for another reason. Patients were approached by letter and phone calls. Once an appointment was made, the patients were reminded of their appointment via cellphone messages. Posters in the waiting room and reception, announcement on the large TV screen in the waiting room and announcement on the practice website supported the awareness campaign. Also the Clinical Commissioning Groups (local NHS organisations) did send a text message to the target and catch-up groups promoting HZ vaccination. Patients were invited at the start of the influenza season to attend the practice on special weekend mornings or afternoons for vaccination (when normally the clinics are shut). If patients were house-bound they were visited and vaccine offered. Patients who refused vaccination were recorded so in the surveillance system. Monthly audits were performed for subsequent waves of reminding invitations.

2.1.3 Outcomes of the UK shingles vaccination programme

In December 2014, PHE published the evaluation of the first year of the HZ vaccination programme in England using HZ vaccine and a summary of the ongoing surveillance activities undertaken by PHE to monitor the impact and effectiveness of the programme.[56]

In the first year of the programme (2013/14), the vaccine was routinely offered to adults aged 70 years on 1 September 2013 and to adults aged 79 on 1 September 2013 as part of the catch-up campaign. Almost 90% (7,107/7,904) of GP practices in England reported annual shingles coverage data for the period September 2013 to August 2014.

Vaccination coverage[56]

Annual shingles vaccine coverage (September 2013 – August 2014) for the routine cohort was 61.8%. This ranged by area team (AT) from 51.3% (London) to 69.5% (Derbyshire and Nottinghamshire), with the majority (19/25) of ATs reporting coverage above 60%. Annual shingles vaccine coverage for the catch-up cohort, i.e. those aged 79 years, on 1 September 2013 was 59.6%. The shingles vaccine coverage data suggests that vaccine coverage for the routine cohort does vary by ethnicity with the White-British and Indian ethnic groups having the highest coverage at 65.7% and 64.0% respectively, and the Black or Black British - any other Black background, and Mixed-White and Black African ethnic groups having the lowest coverage at 41.7% and 43.6%. Vaccination coverage was slightly higher for men when compared to women in both routine (62.1% vs 61.5%) and catch-up (62.5% vs 57.2%) cohorts. The findings highlight the importance of collecting these data in order to describe health inequalities and help target communication and interventions to improve uptake. Nationally, 8.5% of those aged 70 years and 10.7% of those aged 79 years were recorded as having declined the vaccine.

Vaccination in clinical risk groups[56]

In the surveillance system data are also collected on the estimated proportion of patients within the routine and catch-up cohorts who are in clinical risk groups where shingles vaccine may be contraindicated, like patients having a primary or acquired immunodeficiency state due to a medical condition or patients receiving immunosuppressive therapy.[54] Using the surveillance system for coding of clinical risk groups in whom shingles vaccine may be contraindicated, it was shown that an estimated 2.9% of the routine cohort and 3.6% of the catch-up cohort fell into this category. Vaccine coverage in these clinical risk groups for both cohorts was similar to the non-contraindicated group (about 64%). Whether or not a person with a listed clinical risk group on their medical record (as defined by the Read Codes) should receive the shingles vaccine requires a clinical assessment. In some instances these patients are also at particular risk of severe shingles disease and the clinician may decide whether or not the vaccine would be beneficial. It is also possible that although a patient may have a relevant Read Code in their record, the condition that this refers to may have subsequently resolved. Similarly, the patient could at one time have been on a drug that would place them in a risk group, but even though this may no longer be the case the medical record may not have been updated to reflect this.

Vaccine impact and evaluation[56]

The specificity of a clinical diagnosis of shingles will be evaluated through a primary care sentinel surveillance scheme with GP practices recruited from the Primary Care Research Network (PCRN) and the Royal College of General Practitioners' (RCGP) network.

Vaccine effectiveness (VE) against clinically diagnosed shingles and PHN will be calculated using the Clinical Practice Research Datalink (CPRD). A cohort design will be used with those aged 65 to 79 years at the start of the vaccine programme included. Potential confounding variables for adjustment will include age, sex, and period since vaccine introduction and being in a clinical risk group.

Although many patients with PHN are managed in primary care, those with more severe disease are referred to specialist pain clinics for expert advice on pain control. Given the time lag between the development of PHN and referral to a pain clinic, it is anticipated that the data collected in the first year of the programme will serve as baseline data to monitor future trends.

The analysis for effectiveness will require a longer follow-up period as reliable effectiveness estimates can only be calculated once the programme has been in place for a number of years. The same applies to the safety of the vaccine.

Reflection on the success of the national vaccination programme in the UK[56]

Instead of an individual programme, the JCVI in the UK chose for a national vaccination programme because of the significantly increased risk of developing the disease and the significant increased burden of disease in elderly aged ≥70 resulting more frequently in complications such as PHN and an increase in hospital admissions, justifying the avoidance of health inequalities among individuals. Furthermore, analytical studies showed that the most cost-effective age for offering vaccination to prevent and/or reduce the disease burden is for those aged 70 to 79.

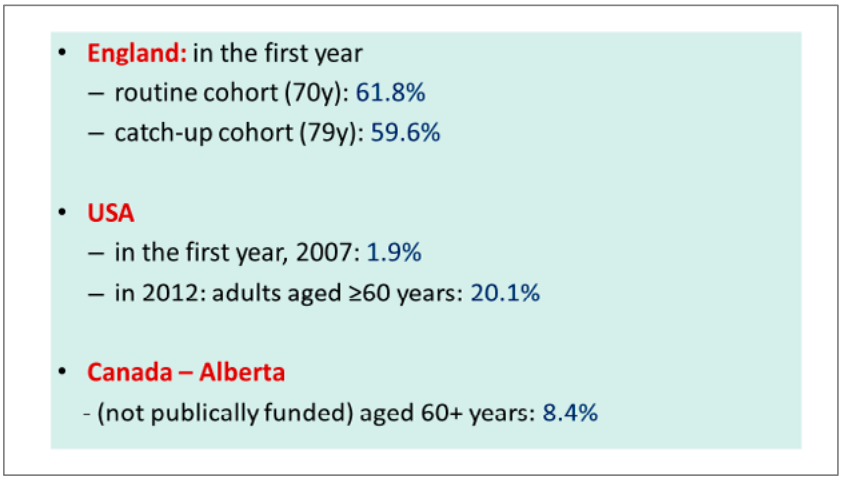
Experience from other vaccination programmes targeting this age group in the UK have demonstrated that it can take several years for a programme to become established and high

coverage to be achieved. For example, for the influenza vaccination programme offered to all patients aged 65 years and above, an increase in coverage in England was observed once the programme had become established, increasing from 65.4% in 2000/01 (the first year of the programme) to over 70% from 2003/04 onwards.[59]

Because the shingles vaccine could be offered to patients alongside seasonal influenza vaccine, most of the eligible cohorts were vaccinated in the first few months of the programme, thus helping to embed the programme and achieve the high coverage of 62% for the routine cohort, and almost 60% for the catch-up cohort in the first year.

The vaccine coverage in England is considerably higher than the individual programme reported in the US in 2012, where 20.1% of adults aged ≥60 years reported receiving HZ vaccination to prevent shingles[60] (in the first year of the US programme, 2007, coverage was 1.9%[61]). Australia and Canada also recommend the shingles vaccine for older adults, but the vaccine is not publically funded, hence coverage is low (estimated coverage in Alberta, Canada was 8.4% for those aged 60+ years from 2009 to 2013).[62 63]

Figure 9: Shingles vaccination rate in the UK, US and Canada.[56 60 63]



2.2 The Comparison between the UK and The Netherlands

2.2.1 The medical need for a shingles vaccination programme

For the assessment of the benefit/risk ratio of shingles vaccination for the elderly population, we align with the statements and facts, published by health authority bodies and reported in guidelines or clinical studies.

Table 4: Statements and facts by health authority bodies and reported in several guidelines and clinical studies.

Body/guidelines/clinical studies	Statement and facts
The UK's Joint Committee on Vaccination and Immunisation (JCVI) recommendation[38] 2010	A national HZ vaccination programme should be introduced provided the vaccine is available at a price that makes the programme economical, for adults aged 70 years with a catch-up programme for those aged 70 to 79 years because of: - the significant increased risk of developing the disease; - the significant increased burden of disease in elderly aged ≥70 years - resulting in complications such as PHN and an increase in hospital admissions; - the justification of avoiding health inequalities among individuals.
The Health Council in The Netherlands[16] 2013	"Efficacious vaccines are now available for the prevention of diseases such as chickenpox, gastroenteritis caused by rotavirus infection, and shingles. However, these are rarely used in the Netherlands. As a result, potential health gains are being left untapped."
Dutch National Health Care institute (Zorginstituut Nederland)[19] 2014	"In the prevention of HZ and postherpetic neuralgia in immunocompetent adults 70 years or older the HZ vaccine has therapeutic added value compared to placebo. The efficacy of the vaccine for the prevention of HZ and PHN is demonstrated. The probability of developing serious side effect is not significantly different between those who have been immunized with the HZ vaccine compared to placebo."
Facts from clinical studies[34 35 36]	The HZ vaccine has demonstrated to decrease the incidence of HZ with 51.3% and to decrease the incidence of the major complication postherpetic neuralgia (PHN) with 66.5% in those aged 60 years and above.[34] The reduction of HZ and PHN in those aged 70 years and above is 38%, respectively 66.8%.[34]
Facts	Despite available antiviral and pain treatment the incidence of HZ and PHN is relatively high. The incidence of shingles increases with age, showing a sharp increase after the age of 50 and showing a sharp increase for PHN at 70 years and above.

Facts[25 26]	Despite antiviral and pain treatment of HZ, the complication PHN is not prevented and once established, adequate analgesic therapy is difficult and referral to a pain specialist or a pain clinic is often recommended. However, none of the analgesic therapies is sufficiently effective.
Facts[17]	PHN is a persistent and difficult-to-treat pain syndrome with a substantial risk to develop serious complications and vaccination can take away or significantly reduce this risk

We conclude that reduction of the incidence of the most common and most severe complication of HZ, i.e. PHN, with 67% in the population ≥70 years of age, when vaccinated with the HZ vaccine, can be judged as 'clinically relevant'. Based on the available evidence, statements and facts, we, therefore, endorse the medical need for a HZ vaccine in the national immunisation programme for the elderly population in The Netherlands.

2.2.2 The rationale for a national shingles vaccination programme in The Netherlands

'National versus individual', a matter of coverage and avoidance of health inequalities

It has been highlighted by the PHE in the UK that the national shingles vaccination programme has achieved a high vaccine coverage in the first year of almost 62% for the routine cohort, and almost 60% for the catch-up cohort.[56] The coverage within an individual programme is usually considerably lower than within a national programme, as is demonstrated in the United States (US), where 20.1% of adults aged ≥60 years reported receiving HZ vaccination to prevent shingles in 2012 (in the first year of the US programme, 2007, coverage was 1.9%).[60]

Shingles vaccine coverage is very similar with the experience from another vaccination programme in the UK targeting this age group, i.e. the influenza vaccination programme offered to all patients aged 65 years and above, in which a coverage of 65.4% in 2000/01, the first year of the programme has been demonstrated.[59] The initial high shingles vaccine coverage is due to the national-wide execution alongside the existing national seasonal influenza vaccination programme and due to the well-established primary care infrastructure in the UK.

We have not extensively described the French structure of shingles vaccination and we did not base our recommendations on the French model for shingles vaccination due to the fact that France is yet about to start the implementation and therefore results about the outcomes are still lacking, and due to the fact that France has implemented an individual vaccination programme. Also, the structure of their primary care differs from that in The Netherlands, while the UK's is similar.

We indicate that the availability of an established primary care infrastructure and the possibility for co-administration of both HZ vaccine and influenza vaccine, provides the 'high way' to high coverage of shingles vaccination. High coverage is required from a health care perspective, given the undisputed medical need. Furthermore, a nation-wide execution justifies the avoidance of health inequalities among individuals.

Rationale for extending the national vaccination programme with shingles vaccination

Currently, there is considerable interest within the European Committee[7 8] as well as within the Dutch government[9] for prevention as a prerequisite for healthy aging due to the demographic growth of the elderly population in Europe, an expected doubling of this population in 2060.[2 3] Knowing that specifically the immune status of elderly populations is deteriorating by natural age, called immunosenescence, and knowing that the high prevalence of chronic conditions[6] among the elderly population weakens the immune response further, timely vaccination is an effective measure for improving the immune status among the elderly. Shingles is a typical consequence of immunosenescence. The reactivation of the dormant chickenpox virus, in a person previously infected with chickenpox, mainly during childhood, is associated with deterioration of the immune status caused of the patient by natural age advancement. This is reflected in the sharp increase in incidence for HZ after the age of 50 and for the severe complication PHN at 70 years and above.
To assess whether shingles vaccination in elderly aged ≥70 years is a suitable candidate for extension of the national vaccination programme for elderly in The Netherlands, we compared the shingles vaccine to the influenza and pneumococcal vaccine (table 5). The parameters used may have an overlap with the criteria set of the Health Council.[16]

Table 5: Comparison of the herpes zoster vaccine, the influenza vaccine and the pneumococcal vaccine.

Expert criteria	Vaccines		
	Influenza vaccine[50]	**Herpes zoster vaccine**	**Pneumococcal vaccine[64]**
Cost-effectiveness per QALY gained	new estimate GR >€20,000 (before €15,500)	€10-29,664 [19 47 48]	€8,650 [65] (age 65-74 years)
Effectiveness	50%	HZ 51.3%; PHN 66.5% (≥60 y)[34] HZ 38%; PHN 66.8% (≥70 Y)[34]	45.6%
Side-effects -local -systemic	Local reaction on injection site Well tolerated	Local reaction on injection site Well tolerated	Local reaction on injection site Well tolerated
Age of vaccination	≥60	70, and catch-up 71-79	>60
Duration of efficacy	1 year	At least 7-10 years	At least 4 years
Experience	≥60 years (since 1953)	± 10 years (since 2006)	No experience yet
Herd immunity	No, due to subpopulation size	No, due to type of disease	No, due to subpopulation size

We conclude that the assessment profiles for shingles vaccine and the influenza vaccine are comparable. Although other preventive programmes, like cervical, breast and colon cancer screening, may be more cost-effective (€9,000, <€2,000-€5,000, respectively <€20,000 per QALY gained), the shingles vaccination programme compares not only well to the influenza vaccination programme but also to the recently introduced prevention programme for 12-year old girls, i.e. HPV vaccination (€18,400 - €30,000 per QALY gained) (see table 3, section 1.4.4).

We conclude that the current evidence of vaccine effectiveness and safety, the cost-effectiveness outcomes and the 10 years of real life experience with the shingles vaccine, combined with the positive outcomes of the national shingles vaccination programme in the UK, justifies the uptake in the national vaccination programme for elderly populations in The Netherlands. Based on analytical studies showing that the most cost-effective age for offering vaccination to prevent and/or reduce the disease burden is for those aged 70 to 79, we suggest to routinely offer the shingles vaccine to adults aged 70 years and to adults aged 71-79 as part of a gradual catch-up campaign. It is also expected that more efficiency can be reached by running two vaccination programmes alongside each other, providing also a better cost-effectiveness for both influenza and shingles vaccination programmes

2.2.3 Implementation of a national shingles vaccination programme in The Netherlands

The structure and organization of the primary care centres in the UK is similar to those in The Netherlands. Based on this primary care infrastructure, both countries have achieved a high vaccination coverage for influenza. As for the UK, the primary care infrastructure in The Netherlands, therefore, provides an excellent framework for shingles vaccination in The Netherlands:

- The extensive experience with the national influenza vaccination programme in The Netherlands, provides an efficient embedding of a shingles vaccination programme alongside the existing national seasonal influenza vaccination programme
- Primary care centres in The Netherlands do have an established communication infrastructure between GP and their patients with regard to vaccination of elderly populations. For patients the role and function of the primary care centre is clear and accepted.
- The population for the influenza vaccination and shingles vaccination do highly overlap.
- The workload for the primary care centre seems comparable for both vaccination programmes.
- The execution of shingles vaccination within the primary care centre has been piloted by Opstelten et al. in 2009.[66]
- The primary care infrastructure provides the detailed individual patient characteristics for assessment of clinical risk groups that are at particular risk of severe shingles disease and should have an adjustment of their immunosuppressive medication for being able to benefit from vaccination. The interdisciplinary contacts between GP's and specialists are so that immunisation is only withheld or deferred where a valid contraindication exists.
- The advantage of a central role of the primary care centre is that one professional is responsible and can be contacted by other professionals.
- The primary care infrastructure facilitates the use of surveillance systems including adverse event reporting.

For the implementation of shingles vaccination in primary care centres it is important, as stressed by Vos et al., 2015, to have a proper discussion with the general practitioners and to secure the financial and logistic support for the execution of the vaccination programme.[67]

The comparability between the primary care infrastructure of the UK and that of The Netherlands, makes it highly likely that the outcomes of the implementation of a national shingles vaccination programme within the primary care infrastructure may also be as successful for The Netherlands. It is also expected that more efficiency can be reached by running two vaccination programmes alongside each other, providing also a better cost-effectiveness for both influenza and shingles vaccination programmes.

2.2.4 Recommendations for a Dutch shingles vaccination programme

Based on strong clinical rationales (the undisputed medical need and therefore the justification for avoidance of health inequality) and societal rationales (demographic challenges, prevalence of comorbidity, immunosenescence, healthy aging and vaccination as effective measure for prevention, as well as the comparability of the HZ vaccine and influenza vaccine in effectiveness, safety and cost-effectiveness), we acknowledge the 'health relevance' of uptake of the HZ vaccine in the national vaccination programme for the elderly population. The already 10 years of worldwide experience with HZ vaccination and the successful example of the UK's HZ vaccination programme, further strengthen our suggestion to the Minister of Health, to align with the UK vaccination programme by extending the Dutch national influenza vaccination programme for the elderly population with HZ vaccination for adults aged 70 years, with a catch-up programme for those aged 71 to 79 years. Whereas co-administration of HZ vaccine and influenza vaccine is feasible, this may provide an opportunity from an organizational as well as from a cost-effective point of view to vaccinate with HZ vaccine and influenza vaccine simultaneously.

Addendum

Addendum

This addendum contains background information for the brief introductory chapters (1.2, 1.3 and 1.4). The A, B and C sections correspond to the chapters 1.2, 1.3 and 1.4 respectively.

A. Introduction to the need for prevention in elderly populations

A.1 Demographic challenge in the European Union and The Netherlands
A.2 Immunosenescence
A.3 Chronic diseases and comorbidity
A.4 Political agenda on 'healthy aging'
A.5 Prevention

B Introduction to vaccination for elderly populations

B.1 Structure of vaccination care in The Netherlands
B.2 Status of vaccination in The Netherlands
B.3 Signalling current challenges

C Introduction to 'herpes zoster vaccination'

C.1 Herpes zoster, the disease, incidence and complications
C.2 Treatment
C.3 Prevention
C.4 Cost-effectiveness of prevention

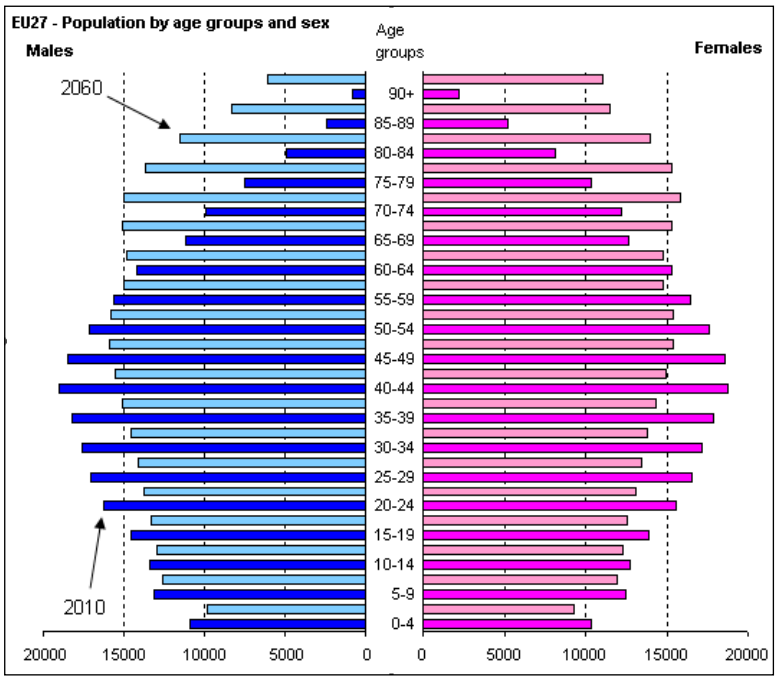
A Introduction to the need for prevention in elderly populations

A.1 Demographic challenge in the European Union and The Netherlands

The European Union (EU)[1]

Due to the expected dynamics of fertility, life expectancy and migration rates, the age structure of the EU population is projected to dramatically change in coming decades (figure 10).

Figure 10: Demographic development in the EU27 from 2010 – 2060.[1]



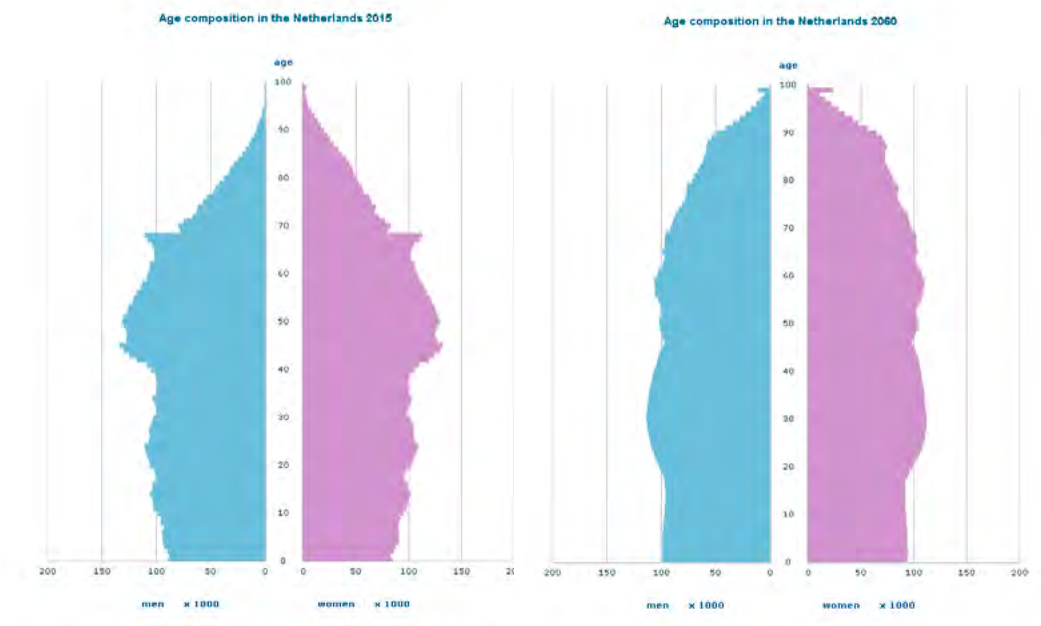
Though the overall size of the EU population is projected to be only slightly larger in 50 years' time (from 501 million in 2010 to 526 million in 2040, with a decline by nearly 2% by 2060), Europe is facing a doubling of the number of people aged 65 and above in the next 50 years, from 87 million in 2010 to 148 million in 2060.[2] The

proportion of young people (aged 0-14) is projected to remain fairly constant by 2060 in the EU27 and the euro area (around 15%), while those aged 15-64 will become a substantially smaller share, declining from 67% to 56%. The population aged 65 and above will rise from 18% to 30% and that of aged 80 and above will rise from 5% to 12%, becoming almost as numerous as the young population in 2060.

The Netherlands[3]

The proportion of young people (aged 0-20) is projected to remain fairly constant by 2060 (0-20 year: 3,827,351 (22.6%) in 2015 to 3,825,603 (21.2%) in 2060), while those aged 20-65 will become a substantially smaller share, declining from 59.6% (10,065,804) to 52.8% (9,538,944). Those aged 65 and above will become a much larger share (rising from 17.8% (3,005,744) to 26% (4,692,778) of the population.

Figure 11: The Dutch population in 2015 and estimated for 2060 (CBS 2015).[3]



A.2 Immunosenescence

Immunosenescence[4 5] refers to the gradual deterioration of the immune system brought on by natural age advancement. This age-associated immune-deficiency is ubiquitous and found in both long- and short-living species as a function of their age relative to life expectancy rather than chronological time. It is considered a major contributory factor to the increased frequency of morbidity and mortality among the elderly.

A.3 Chronic diseases and comorbidity

Chronic diseases[6]

'Chronic diseases' are defined as irreversible disease with no prospect of full recovery and a relatively long disease duration. A chronic disease is further distinguished by a lengthy appeal to care. In the Netherlands almost a third of the population (5.3 million people) has one or more chronic diseases. This estimate is based

on the National Primary care practice Information Network (Dutch: Landelijk Informatie Netwerk Huisartspraktijken, LINH), in which 28 different chronic diseases are registered. The RIVM selected these 28 chronic diseases based on an Australian Primary Care Study on Chronic diseases and matching these diseases with the chronic diseases in The Netherlands.

Table 6: Chronic diseases selected by the RIVM (ranked by ICPC-1 code).[6]

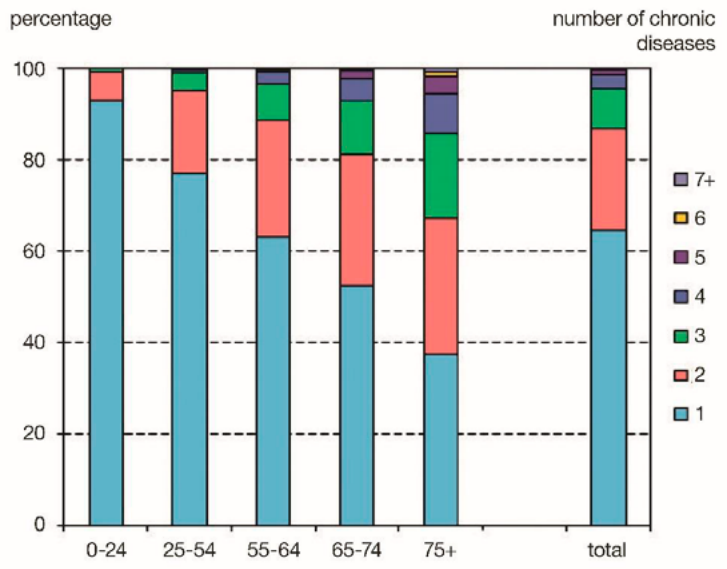
Chronic disease	ICPC-1 code	Chronic disease	ICPC-1 code
Aids and HIV-infection	B90	Parkinsonism	N87
Cancer	A79, B72, B73, D74,A79,B72, B73, D74, D75, D76, D77, L71, N74, R84, R85, S77, T71, U75, U76, U77, W72, X75, X76, X77, Y77, Y78	Epilepsy	N88
Visual disturbances	F83 Retinopathy, F84 Macular degeneration, F92 Cataract, F93 Glaucoma, F94 Blindness	Migraine	N89
Hearing disorders	H84 Presbyacusis H86 Deafness	Chronic alcohol abuse	P15
Congenital anomaly, cardiovascular	K73	Dementia	P70
Rheumatic fever heart disease	K70-71/heart valve disease K83	Schizophrenia	P72
Heart failure	K77	Mood disorders	P73 Affective psychosis P76 Depressive disorder
Coronary heart disease	K74 Ischaemic heart disease with angina, K75 Acute myocardial infarction, K76 Ischaemic heart disease without angina	Anxiety disorder/anxiety state	P74
Heart Rhythm disorders	K78 Atrial fibrillation/flutter, K79 Paroxysmal tachycardia, K80 Cardiac arrhythmia	Neuraesthenia, surmenage (burn-out)	P78
Cerebro vascular disease	K89 Transient cerebral ischaemia, K90 Stroke/cerebrovascular accident	Personality disorder	P80
Rheumatoid/sero positive arthritis	L88	Mental retardation	P85
Peripheral arthrosis	L89 Osteoarthritis of hip L90 Osteoarthritis of knee L91 Osteoarthritis, other	Chronic obstructive pulmonary disease	R95
Chronic neck- and back disorders	L83 Neck syndrome L84 Back syndrome without radiating pain L86 Back syndrome with radiating pain	Asthma	R96
Osteoporosis:	L95	Diabetes non-insulin dependent	T90

Chronic diseases occur at all ages, but especially among the elderly. In The Netherlands among people aged 65 and above, 70% have a chronic illness. In people aged 75 and above, this percentage is 79%. Among the people aged 65, women more than men have a chronic disease.
The rates for chronic diseases in the whole of Europe are more or less comparable, though slightly higher.

Comorbidity[6]

Thirty-five percent of people with chronic illness has more than one chronic disease (based on the same selection of 28 diseases). This equates to 1.9 million people or 11% of the total Dutch population. Of people aged 75 and above, half has more than one chronic disease. In people aged till 74 years, multimorbidity is slightly more common in women than in men. However, in people aged 75 years and above, there is hardly any difference between men and women. Of people with chronic illness, 65% had one chronic disease, 22% had two chronic diseases, 8% and 5% three or four more. This distribution varies widely between age groups. Of people aged 75 and above half has more than one chronic disease, 63% had two or more chronic diseases, and 32% three or more (figure 12). The rates for chronic diseases and comorbidity in the whole of Europe are more or less comparable, though slightly higher.

Figure 12: Distribution of the number of chronic diseases among patients with a chronic illness.[6]



Quality of life in chronic diseases and multimorbidity[6]

People with a chronic disease have a poorer quality of life compared to healthy individuals. Depending on the nature and severity of the diseases, multimorbidity may have an additional negative effect on the quality of life. People with multimorbidity are hospitalized more frequent and longer and more likely tend to have more complications after surgery and an increased risk of premature mortality.

A.4 Political agenda on 'healthy aging'

European Commission[7 8]

Beside one of the most serious challenges of demographic ageing (an almost doubling of the number of persons aged 65 and above in the next 50 years), also the amount of elderly suffering from a chronic disease and even multimorbidity attributes to this challenge. It is clear that the EU and individual member states are highly concerned about managing the health care issues for the elderly populations. The demographic trend

represents a challenge for public authorities, policy makers, businesses and the non-profit sector, especially as it comes at a time of increasing pressure on public budgets, a steady decline in the number of health personnel and growing demands from older people for care products and services. If this demographic transition is not tackled head-on, it will cause serious problems in relation to the financial sustainability of health and care systems. Public spending on health already accounts for 7.8% of GDP in the EU, and by 2060, public expenditure on acute health care and long-term care is expected to increase by yearly 3 % of GDP due to aging. Supporting active and healthy ageing is important both to improve the quality of life of the elderly population and help them contribute to society as they grow older and to reduce unsustainable pressure on health systems. It is therefore necessary to improve employment opportunities and working conditions for older workers, but also to improve their inclusion in society and to encourage healthy aging.
The European Innovation Partnership on Active and Healthy Aging has been selected by the European Commission to tackle the challenges presented by an aging population. This initiative is part of the flagships initiatives of the Europe 2020 strategy with the objective of accelerating innovation to address a well-defined target within a grand societal challenge. The targets of this initiative are increasing the average healthy lifespan of EU citizens by 2 years by 2020, and pursuing a triple win for Europe by improving health and quality of life of older people, improving the sustainability and efficiency of care systems and creating growth and market opportunities for businesses. The health and quality of life of older people focuses on actions developed around 3 pillars: prevention, screening and early diagnosis; care and cure; and active ageing and independent living.

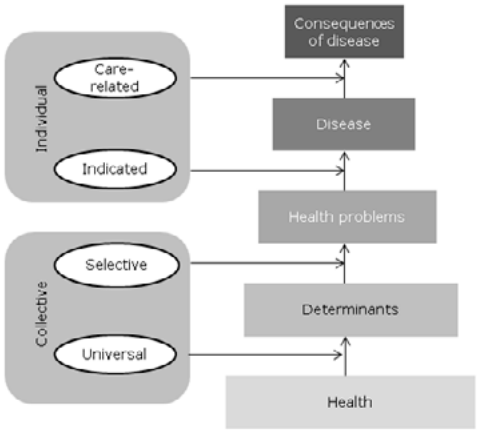
Dutch political agenda[9]
In January 2007, the Dutch parliament has adopted a resolution 'Van der Veen et al (30800-XVI, no. 74)', which argues that more health related prevention leads to better health, that there is too little focus on prevention, that insurers play an important role in prevention and that there are insufficient incentives to develop preventive activities. Subsequently, the Second Chamber of parliament has requested the government, to determine whether and how prevention in the basic insurance package can be integrated. At the end of 2013 the Ministry of Health and five other ministries presented in a joint action with five other ministries, the 'National Prevention Programme 2014-2016' (NPP) to the Dutch parliament. This joint programme aims to sustainably protect public health from threats and where it can improve further. A more prominent place for prevention in healthcare is one of the primary goals of the NPP. Other goals include: promoting 'healthy aging' through a healthy environment and the maintenance of health protection. Additionally two worrying trends are pointed out: the health differences between lower and higher educated – social classes- are large and the population is aging in combination with the increasing number of chronic diseases per person. Likewise the European Committee the NPP addresses the attention for the quality of the individual's life, and also for participation in society and in employment. The objectives of the NPP are translated into a programme in three areas: 1. Health integrated in the environment in which people live, work and learn, 2. Give prevention a prominent place in healthcare programmes and 3. Maintain Health Protection, new threats facing.
Furthermore, the first 6 month of 2016, the Ministry of Health will fulfil the role of Chairman of the EU. One of the goals in the Dutch programme is to diminish the use of antimicrobial medicinal products within the EU.[10] Vaccination may be a useful strategy to reach this goal.[11]

A.5 Prevention

Technical framework of prevention[12]
The definition of prevention is the prevention of disease and the protection and promotion of health. The goal of prevention is to ensure that people stay healthy by promoting their health and protecting their health. Also,

prevention aims to prevent disease and complications of diseases at the earliest possible stage of detection. There are four broad classifications of prevention in use, namely
1: target audience (universal prevention actively promotes and protects the health of the healthy population; selective prevention tries to prevent individuals with one or more risk factors (determinants) for a particular disorder or illness; indicated prevention tries to prevent incipient symptoms of a condition; care-related prevention tries to prevent an existing condition before it leads to complications or limitations, a lower quality of life or death),
2: stage of the disease (primary prevention includes activities that prevent healthy people from a certain health problem, illness or accident; secondary prevention includes activities that prevent diseases or abnormalities that are detected at an early stage in people who are ill and/or in people that have an increased risk of a genetic predisposition; tertiary prevention, the target group consists of patients, includes activities to prevent complications and disease exacerbation),
3: type of measure (disease prevention, health promotion and health protection), and
4: method of execution (involves the following five pillars: installation of the physical and social environment, such as: smoking in schoolyards; regulatory enforcement, such as laws, permits; information and education to groups, such as: group education; identification and individual advice, such as: consultation on prevention, signalling overweight at school, national screening programmes); support, such as short-term personal support).

Figure 2: Classification of prevention.[12]



Legal framework of prevention[12]

Prevention in the Netherlands is regulated by law. The Public Health Act (Dutch: Wet publieke gezondheid, Wpg) and the Law on Population Screening (Dutch: Wet op het bevolkingsonderzoek, Wbo) form the main legal framework to protect and promote the health of the population. The national government has the constitutional task (Article 22, Health Insurance Act) to take measures to promote public health. The Minister of Health is responsible for formulating policy objectives and activities and for activating actors for a targeted, effective and efficient execution of tasks. In addition to the Ministry of Health, other ministries play a role in prevention. The Ministry of Social Affairs and Employment (Dutch: Sociale Zaken en Werkgelegenheid, SWZ) plays an important role in protecting and promoting the health of the working population. The Ministry of Infrastructure and Environment (I&M) is partly responsible for the prevention of environmental health and safety. The Ministry of Economic Affairs, Agriculture and Innovation (ELI) is partially responsible for food safety. The basis for the Dutch health is written down in the 'prevention cycle'. This is a four year policy laid down in the Wpg. The RIVM updates every four years, the Health Future Study (Dutch: Volksgezondheid Toekomst Verkenning, VTV)[49]. This survey gives a picture of the status of health in the Netherlands, amongst others on the basis of epidemiological data. Based on this survey, the Minister of Health formulates a national health policy with the priorities in the field of public health. In 2011, the latest nation-wide health policy report was published. Lastly, the Healthcare Inspectorate monitors the implementation of the health policy and publishes the 'Health of the State'.

Financial framework of prevention

European Union:[2] Although prevention has been proclaimed as the key priority for health systems, yet, less than 3% of the actual health budgets in both the entire EU and Netherlands is dedicated to promotion and prevention activities. This is particularly important in the context of demographic change, because prevention can result in better health, higher quality of life and slower functional decline for older people. The EU also addresses primary prevention through targeting the key health determinants of chronic diseases by strategies (nutrition and physical activity, alcohol consumption), action plans (cancer) and communication campaigns (smoking). Despite the positive development of a move away from vertical disease specific programmes and towards an integrated approach to chronic diseases, the major problem remains the unbalanced nature of health spending, 97% on curative services and just 3% allocated to prevention and promotion activities. This is despite the strong evidence on the efficacy of prevention (primary, secondary and tertiary) and its cost effectiveness. Thus, there is an urgent need for policy change.

The Netherlands:[12] In 2007 an estimated 13 billion euro was spent on prevention in the Netherlands. The majority, 10 billion is spent outside care. Almost all expenditure is spent outside the health-care protection, such as the fight against air pollution and promoting road safety. Around 3 billion is spent in care, of which the majority (2.5 billion euros) is appointed to disease prevention, such as vaccination, screening and preventive medication. To health promotion measures such as lifestyle education about half a billion is spent.

ZINL is of the opinion that universal and selective prevention are collective forms of prevention (focus on populations) that need to be paid by the municipal or national government. Indicated and care-related prevention aim at individuals and therefore fall under the Health Insurance Act.

B Introduction to vaccination for elderly populations

B.1 Structure of vaccination care in The Netherlands

In The Netherlands, vaccination practice is organized through a public programme (National Immunisation Programme, NIP; Dutch: Rijksvaccinatieprogramma, RVP), a health insurance programme (Health Insurance Act; Dutch: Zorgverzekeringswet, Zvw) and a free programme (table 1).[13]

Table 1: Overview structure, financing and implementation structure of vaccination.[13]

	Public Programme (NIP, RVP)	Health Insurance Act (Zvw)	Free market
Decision for admission	Ministry of Health	Ministry of Health	Ministry of Health
Advisory Board	HC	ZINL	ZINL
Financing structure	Special budget of the Ministry of Health	Collective budget health insurances	Out of pocket
Type of care	Prevention	Indicated Care	Prevention
Implementation	Special public institutes or GP practice	In general GP practice	Special private organisations

The different programmes will be discussed below as well as their financing and implementation structure.

Public programme or National Immunisation Programme (NIP)[13]

In The Netherlands most vaccinations are offered through public vaccination programmes: the NIP for children and the national influenza vaccination programme destined for people who are aged ≥60 or for those who are under 60 and have a medical indication for influenza vaccination.

The government has an active and leading role in these two programmes. The Minister of Health determines the content of the programmes. Since 2005, management of the programmes has been the responsibility of the Centre for Infectious Disease Control (Dutch: Centrum Infectieziekte-bestrijding, CIb), part of the National Institute of Public Health and the Environment (Dutch initials: RIVM). Finally, the Health Council (HC) plays an advisory role in relation to all these activities. The Health Council identifies and assesses scientific information about vaccination and makes appropriate recommendations regarding the scope and content of the NIP. The RIVM then purchases the vaccines and distributes them to the executing parties. People receive an individual call for the vaccination of themselves or of their children vaccinated and when they do not appear, they receive a reminder. This approach is efficient and leads to a high vaccination coverage.

The Health Council, established in 1902, is an independent scientific advisory body with the task 'to advise the government and parliament on the level of knowledge regarding issues of public health' (Article 22, Health Act). Because of the importance of an independent opinion, the Minister of Health requests advice of the HC regarding the content and composition of the public vaccination programme. To be able to perform this task well, the Health Council installed a 'Commission NIP' in 2001. In 2014 this was replaced by a permanent committee Vaccination.

Till 2007, there was no standard national or international framework for the assessment of vaccines. In their report of 2007, the HC published an assessment framework of seven criteria to support decision-making and prioritisation for the provision of a given form of vaccination for a given group (table 7).[15]

Table 7: Seven criteria for the assessment of vaccines defined by the Health Council.[15]

1 The infectious disease causes considerable disease burden within the population.
- The infectious disease is serious for individuals, and:
- The infectious disease affects or has the potential to affect a large number of people.

2 Vaccination may be expected to considerably reduce the disease burden within the population.
- The vaccine is effective for the prevention of disease or the reduction of symptoms.
- The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought).

3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

4 The inconvenience or discomfort that an individual may be expected to experience *in connection with his/her personal vaccination* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

5 The inconvenience or discomfort that an individual may be expected to experience *in connection with the vaccination programme as a whole* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

In conclusion, the HC includes aspects such as the severity of the disease, incidence of the disease and the effectiveness and efficiency of vaccination. The HC also takes into consideration the health effects (both positive and negative) of others than the target population vaccinated.

Until recently there were almost exclusively licensed vaccines on the market that protected against relatively serious diseases. Vaccination aimed, in addition to the protection of the individual, also prevention of epidemics. The latter is a public interest. The programmatic approach through public vaccination programmes is justifiable when it comes to the prevention of serious diseases and when, from the viewpoint of prevention of epidemics, it is important to achieve high vaccination coverage.

<u>The Health Care Insurance Act (Dutch: Zorgverzekeringswet, Zvw)</u>
Another system, through which vaccines may become available is the collective finance of regular care, the Health Insurance Act. A manufacturer may apply directly for reimbursement of a vaccine.
The National Health Care Institute (Dutch: Zorginstituut Nederland, ZINL) advises in his role as gatekeeper for the Health Insurance Package under this Health Insurance Act. ZINL has developed an own assessment framework based on the criteria of the Health Insurance Act. In addition to elements such as the effectiveness and efficiency of vaccination, also, elements such as necessity and feasibility are considered. For care funded by the Health Insurance Act, the principle applies that the insured must be *indicated* for the care. In its report on prevention[68] ('Van preventie verzekerd', 2007) ZINL speaks of '*indicated*' prevention. Among indicated prevention is the care that aims to prevent the occurrence of disease in an individual with an increased risk for that disease. In particular, in the prevention, there is often no direct indication for care. Given the nature of the Health Insurance Act and its analysis with regard to the place of prevention within the Health Insurance Act

(Zvw), it is conceivable that ZINL will advise cautious about admitting vaccines. When a vaccine is admitted in the insured package of the Health Insurance Act, the government does not organize an individual call for vaccination and send no repeat call. Also the government does not contract a healthcare provider but the health insurer does. The decision whether or not to approach the (family) doctor for vaccination has to be taken by the vaccinee.

Out-of-pocket

Besides the two options for vaccination care, as discussed above, vaccines are available on the free market. Insurers may choose to include this in a supplementary health insurance package. To date there is little use of this possibility, probably because it still involves a limited number of vaccines and because doctors and the general public have insufficient knowledge about these vaccines. A positive exception is the travellers vaccines.

B.2 Vaccination status in The Netherlands

Status of the public vaccination programme: National Immunisation Programme (NIP)[15]

The general objective of the NIP is protection of the public and society against serious infectious diseases by vaccination. There are three ways of achieving this objective. The first is the eradication of diseases. This is feasible for some diseases (as seen with polio and smallpox), but not in all cases. Where eradication is not possible, the achievement of group or herd immunity is the
next objective. This involves achieving a level of immunity within a population, such that an infectious disease has very little scope to propagate itself, even to non-immunised individuals. To this end, it is necessary to achieve a high general vaccination rate. If this second strategy is not feasible either, the third objective is to protect as many individuals as possible. Since 1957, Dutch children have been vaccinated against infectious diseases through the National Immunisation Programme (NIP), usually at clinics for infants and toddlers.

National Immunisation Programme (NIP) for toddlers and children

The NIP targets, because of its public nature of the protection, the entire population. However, where disease is unevenly distributed across the population to protect the population as a whole, it may be efficient to focus on vaccination of one or more specific groups or subpopulations. In fact, this is the case for vaccination of infants and young children. The target diseases of the NIP, are to a large part diseases that especially arise in children and particularly in this subgroup can lead to serious illnesses. The NIP makes a very considerable contribution to the prevention of death and disease among children. Initially, vaccination was provided against diphtheria, whooping cough, tetanus and polio only. Later, the programme was extended to also provide protection against measles, German measles, mumps, hepatitis B, and infection by *Haemophilus influenzae* type b, meningococcal C, pneumococci and human papilloma virus. At present, the vaccination rate achieved by the NIP is more than 95 per cent. However, there are differences in vaccination rate among different ethnic groups and religious/philosophical groups.

National Immunisation Programme (NIP) for Elderly populations

This programme is destined for people who are aged ≥60 or are under 60 years of age and have a medical indication for influenza vaccination. Although the national influenza vaccination programme is not organised through the NIP for children, but through primary care centres, the objectives of both programmes are similar.

B.3 Signalling current challenges

To optimise the introduction of new vaccines, the vaccination care models and national vaccination programmes were reviewed by the HC. Signals and suggestions were provided by the HC to the Ministry of Health in their report 'The individual, collective and public importance of vaccination' (2013).[16] Individual experts and the Minister of Health reacted in writing on the signals of the HC. The signalling from HC, individual experts and Minister of Health is discussed below.

Health Council signals: New vaccines and new target groups require consideration[16]

The NIP was originally set up to combat childhood illnesses. The past few years, however, more and more expansion to other age groups is seen, for example the National Influenza Vaccination Programme. According to the HC in its report of 2007[15] the NIP will increasingly become a programme for all age groups. It is expected that older people will be increasingly a target for public vaccination programmes. For this reason the HC has assessed the merit of providing various age groups with vaccination against each of a variety of conditions in the context of a public vaccination programme. In fifteen of the twenty-three vaccine-cases considered, the HC concluded that the disease burden was considerable and that provision of the vaccination in a public programme could therefore be desirable. Furthermore, the HC saw an urgent need to evaluate vaccination chickenpox, hepatitis B, intestinal rotavirus infection and cancer resulting from human papilloma virus (HPV) infection. In the meantime, of these subjects only the vaccinations for hepatitis B for babies and for HPV for girls 12 years of age have been added to the national programme. In 2013[16], the HC reported that efficacious vaccines are available for the prevention of diseases such as chickenpox, gastroenteritis caused by rotavirus infection, and shingles, but that these are rarely used in the Netherlands and therefore potential health gains are being left untapped.

Providing therapeutic vaccines

It is likely that in the future also vaccines against non-infectious diseases will become available, such as vaccines against, amongst others insulin-dependent diabetes mellitus, multiple sclerosis, melanoma, and rheumatoid arthritis. In these circumstances the disorder is already present and vaccination can be considered as a therapeutic option. The HC believes that such a therapeutic use of vaccines does not fit within a general public programme for the prevention of disease as the NIP. This also applies to vaccines which are being developed to support smoking cessation. The use of such vaccinations belongs, when they become available, to the responsibility of the individual.

Health Council signals: Problems with current vaccination structure[16]

To prevent under-utilization of vaccines, it is important to anticipate on how the assessment and accessibility of new vaccines in the future can be ensured. Beside vaccines for serious infectious diseases, increasingly new vaccines come on the market that protect against less severe illnesses and/or predominantly have an individual interest. This may decrease the willingness of the population to participate in public vaccination programmes. The HC recalls in this context societal discussions about vaccination against cervical cancer, pandemic influenza and seasonal influenza. The HC also sees the Health Insurance Act as the place to give individuals access to preventive interventions that are considered to be essential care, but which serve no obvious public interest. Though the Minister of Health decides about the admission of vaccines in both the NIP and in the Health Insurance Act, the different advisory bodies, i.e. the HC and the ZINL are responsible for assessment of the vaccines partly based on different assessment criteria. This structure brings the risk that both advisory bodies consider the evaluation of vaccines, reject an effective and efficient vaccine because it does not fit within their respective framework of assessment criteria. To overcome current problems and to adequately admit new vaccines, the HC has reported 7 recommendations to the Minister of Health (table 8).

Table 8: Seven recommendations of the HC to the Ministry of Health.[16]

Recommendations	
1	There should be a single general framework for all vaccinations in the whole spectrum of vaccination care. -Initially, assessment takes place for defining whether a vaccine opts for collective financing **Criteria for essential care** *Severity and extent of the burden of disease* 1 The (infectious) disease causes considerable individual burden of disease. *Efficacy and safety of vaccination* 2 Vaccination leads to a significant reduction of the burden of disease: the vaccine is effective in the prevention or reduction of symptoms of disease. 3 Any adverse health effects of vaccination (side effects) do not significantly detract from the health benefit. *The efficiency of the vaccination* 6 The ratio between the cost and health benefit is favorable in comparison with other possible options to reduce the burden of disease. These criteria are the modified criteria 1, 2, 3, and 6 that are used for assessment whether a vaccine is included in the NIP.
	-Thereafter, assessment for inclusion in a public program takes place by reference to the existing seven criteria **Seven assessment criteria of the Health Council for inclusion in the NIP (see also table 7)** 1 The infectious disease causes considerable disease burden within the population. • The infectious disease is serious for individuals, and: • The infectious disease affects or has the potential to affect a large number of people. 2 Vaccination may be expected to considerably reduce the disease burden within the population. • The vaccine is effective for the prevention of disease or the reduction of symptoms. • The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought). 3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit. 4 The inconvenience or discomfort that an individual may be expected to experience *in connection with his/her personal vaccination* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole. 5 The inconvenience or discomfort that an individual may be expected to experience *in connection with the vaccination programme as a whole* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole. 6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden. 7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.
2	The scientific advice for the entire spectrum of care vaccination best be administered by the HC. Reconciliation with the Care Institute Netherlands on the criteria for inclusion of vaccinations in the insured package is self-evident or necessary.

3	The Health Insurance Act is the place for individuals to provide access to preventive interventions that have become as essential care considered but that does not serve a clear public interest.
4	The seventh criterion (urgency) may serve to determine whether a programmatic implementation is necessary, what assurances from public perspective should be built and which arrangements therefore must be made with the health care provider.
5	It should be investigated whether it is possible to increase the effectiveness of vaccines financed collectively by realizing economies of scale.
6	There is structural attention needed for vaccinology and related discussion and information skills training and retraining of nurses and doctors in child health care, general practitioners, general practitioners, paediatricians and internists.
7	The public information on vaccines and vaccinations should be strengthened. The RIVM is the appropriate party to be responsible for informing the public about the whole spectrum of care vaccination.

Individual signalling[17]

Recently, individual experts on public vaccination, Verweij et al. 2014, published their ideas about the responsibility of the government with respect to vaccination. They consider the general assessment framework of the Health Council too general and insufficient. They present two additional basic ethical principles that explain why certain vaccinations are the state's moral-political responsibility, and that may further guide decision-making about the content and character of immunisation programmes. Their first principle states that the state is responsible for protecting the basic conditions for public health and societal life. The spread of infectious diseases can have severe effects on communal life and protection against such infections is necessary for a flourishing society. This is most clear in case of a large outbreak of a dangerous disease like measles or tuberculosis. In many cases, collective vaccination will offer such protection most effectively.
The second consideration guiding government's responsibility for public health is justice. They consider this principle not only as a principle for fair distribution, e.g. among subgroups, of the benefits of vaccination, but also as a principle that would guide choices as to why the state should offer certain vaccinations. The idea that all citizens should have equal access to basic health care is shared widely, and indeed most industrialised countries have some form of universal health care coverage. There is no reason to limit this idea to patient care and not also include certain preventive vaccinations. In order to promote fair equality of opportunity the state should create equal access to vaccinations that are necessary for individual persons or subgroups of the population to maintain health. If persons or these subgroups run substantial risk to develop a serious disease, and vaccination can take away or significantly reduce the risk, it might be unfair if some can afford vaccination and others cannot. If so, the state has moral reasons to offer equal access to this vaccination – of course within the limits of reasonable health care expenditures. The authors argue to include these principles in the decision-making on admittance of vaccines within the current vaccination structure.

Minister of Health signals[13]

The Minister of Health confirms the signalling of the Heath Council that potential health gains are being left untapped due to not using current registered vaccines. A major cause of this problem is that increasingly new vaccines are entering the market that do not obviously qualify for programmatic offerings. Vaccines with an individual medical indication (indicated care) are currently covered under the Health Insurance Act. However, vaccines, not for indicated care, currently are not covered by the Health Insurance Act (Zvw). In anticipation of solving problems within the current structure and in anticipation of the arrival of new vaccines, the Minister of Health has proposed a new vaccination-care model. This model aims for an integrated procedure and advice by

both the HC and ZINL about all new vaccines and to form a Review Chamber Vaccines (Dutch: 'Beoordelings Kamer Vaccins', BKV). Moreover, the formal partnership between the two bodies needs to result in recommendations about the target population (individuals or subgroups) for which the vaccine would be (cost-) effective and efficient and about the positioning of the vaccine in the health system. Subsequently, it is up to the Minister of Health to decide about the positioning and admittance of vaccines. Concerning the hew vaccination-care model, the Minister does expect that only for the uptake of vaccines in the Health Insurance Act, the procedures and assessment regulation needs to be adjusted, but this does not require a change in law. For the National Programme, the Minister has changed the law (Wpg) for integrating this Programme and at the same time for generating the possibility to integrate new vaccines for subgroups into the National Programme.

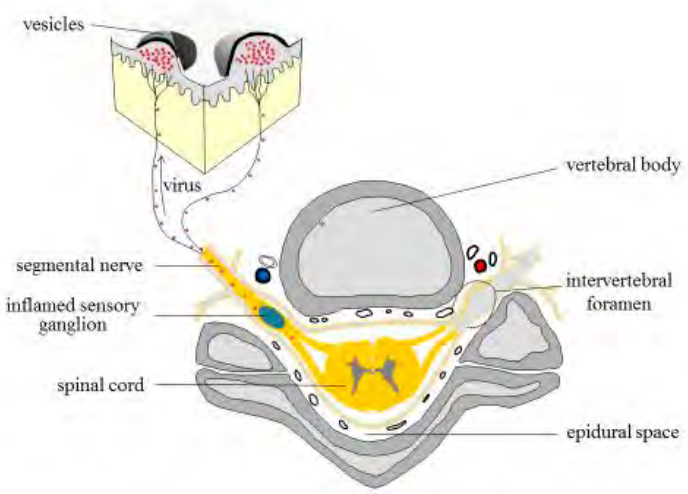
C Introduction to 'herpes zoster vaccination'

C.1 Herpes zoster, the disease, incidence and complications

Pathophysiology[18 19]

The acute phase, herpes zoster (HZ), commonly known as shingles, is caused by the reactivation of the varicella-zoster virus (VZV), the virus that causes chickenpox mainly during childhood. After recovery from chickenpox, the virus remains dormant in sensory ganglia (figure 3[20]). Therefore, HZ can only occur in people who have had a prior infection with VZV. Because human virus-specific cellular immunity gradually weakens during aging (immunosenescence), the virus can, at a certain point, overcome its host defence barriers. It then spreads from the ganglion, via the axon, to the skin and causes the characteristic one-sided vesicular rash in one or, sometimes, a few dermatomes (figure 3).

Figure 3: Schematic representation of the position of the sensory ganglion in the spinal column and the transportation of the virus via the segmental nerve (drawn by G.J. Groen and A.J.M. van Wijck).[20]



Clinicians must be aware of sight-threatening eye disorders when shingles occurs in the first branch of nervus trigeminus, i.e. when cutaneous lesions are present within the area of the nervus nasociliaris, which includes not only the tip of the nose, but also the side of the nose and the medial corner of the eye. This may lead to herpes zoster ophthalmicus (HZO).

Since the vesicles contain the virus, they are contagious for individuals who have not yet formed natural immunity against the pathogen. For example, grandparents with shingles can be the source of chickenpox suffered by one of the grandchildren or any other non-immune to VZV. However, children with chickenpox cannot cause shingles in adults. The subacute herpetic phase refers to pain that persists beyond the healing of the rash, and may persist from 30 days to several months after the initial onset of the rash. Finally, postherpetic neuralgia (PHN) is the phase of chronic pain and refers to pain persisting beyond 3-4 months from the initial onset of the rash. It can last for many years.

Incidence

Incidence of HZ [18] [19]

Recent studies conducted in Europe estimate an overall annual incidence of HZ of 2.0 - 4.6 cases per 1,000 persons. The incidence is highly age-dependent. HZ is uncommon in children and young adults unless immunosuppressed. Age-specific HZ incidence rates are at around 1/1,000 in children to adults <40 years, around 1–4/1,000 in adults aged 40–50 years. A sharp increase after 50 years is reported to around 7–8/1,000 up to 10/1,000 at 80 years of age and above. HZ is more common in women than men.

In The Netherlands, the annual incidence of HZ based on GP consultations amounted to 3.2 – 3.3 (average 3.25) per 1,000 in the period 1998–2001.[69] According to a study focused on gender differences, HZ incidence in females was 3.9/1,000 patients/year (95% CI 3.6–4.2), and in males, 2.5/1,000 patients/year (95% CI, 2.3–2.8).[70] ZINL refers to the Second National study, executed by NIVEL/RIVM, showing the following figures on the annual incidence and prevalence of HZ (data from May 1, 2000 to April 30, 2002) in different age categories.[71]

Table 9: Incidence and prevalence of HZ in The Netherlands.[71]

Age category			All ages		45-64 yr.		65-74 yr.		≥75 yr.	
Herpes zoster (ICPC S70)	N (abs)	N/1.000	M	F	M	F	M	F	M	F
Incidence	1115	3.0	2.4	3.5	2.9	5.8	4.8	5.7	7.3	8.4
Prevalence	1421	3.8	3.1	4.5	3.8	7.0	7.6	7.6	10.5	12.1
N (abs): the absolute number of new episodes (incidence) respectively patients (prevalence) in the study population. M: man; F: female. Except for N (abs) all data are 1.000 persons per year.										

Incidence of PHN

The main risk factors of PHN are the age and in particular the patients aged above 60, the severity of acute pain and the severity of the rash at presentation. Despite early administration of anti-viral therapy, the incidence of PHN varies between 9% in 60-64 years of age to over 50% in persons >80 years of age.[23]

In a study conducted on general practice research database information in The Netherlands emerged the risk of developing PHN 1 month and 3 months after HZ is demonstrated.[72] Estimates for PHN at 3 months were based on few cases.

Table 10: Incidence and prevalence of PHN in The Netherlands.[72]

Age groups % PHN (95% CI)	1 month	3 months
45-54	3.9 (1.3 – 9.0)	0.8 (0.02 – 4.3)
55-64	36.5 (3.0 – 11.9)	2.9 (0.8 – 7.2)
65-74	10.7 (5.2 – 16.3)	3.3 (0.9 – 8.3)
75+	18.0 (11.5 – 24.6)	9.0 (4.8 – 15.2)

Incidence of HZO

HZO incidence ranges from 9-16% of all HZ cases, and as for HZ incidence, it increases with age.[21]
For The Netherlands, a significant association among PHN at 1 month and ophthalmic localization emerged in Opstelten et al., 2002 (OR 2.3, 95% CI 1.0-4.6).[72]

Higher incidence of HZ among chronic diseases[18]

Besides age, the risk of HZ increases significantly in presence of chronic conditions. They include allergic rhinitis, chronic obstructive pulmonary disease, coronary artery disease, depression, diabetes mellitus, gout, hyperlipidaemia, hypertension, hypothyroidism and osteoarthritis. Chronic cardiovascular diseases occur in 54.7% of patients while chronic respiratory diseases in 12.6%. Wu et al., 2015, demonstrated the increased risk of HZ in patients with heart failure based on a population-based study in Asia.[73]
Patients with disorders of cell-mediated immunity (due to disease or medical interventions) are at increased risk for development of HZ. Those patients are at risk for VZV dissemination and visceral organ involvement. A recent review of Westra et al., 2015, reported on vaccination of patients with autoimmune inflammatory rheumatic diseases (AIRDs).[22] These patients are also at increased risk of HZ. Most immunosuppressive therapies and therapeutic biologic agents exacerbate the incidence. Prospective cohort studies of patients with RA have found a wide range in the incidence of HZ (0.55-12.1 cases per 1,000 patient-years). RA is a risk factor for HZ (HR 1.65–1.91, compared with healthy individuals). Treatment with immunosuppressive drugs, except etanercept and methotrexate, increases this risk. The risk of patients with SLE contracting HZ is also increased (5-fold to 16-fold), compared with the general population. However not only HZ but also influenza, pneumococcal and human papillomavirus (HPV) infection cause complications more frequently in these patients than in the general population. Premature 'aging' of the immune system in patients with immune-mediated diseases might be responsible for deterioration of important immune functions, and therefore a reduced protection from infections.
Most of the available vaccines for infections are effective in preventing disease in patients with an AIRD, even those patients who are treated with immunomodulatory therapies. However, treatment with rituximab, and probably abatacept, can suppress immune responses after vaccination. According to Westra et al., 2015, it is important to address the vaccination status in daily practice in the initial work-up of patients with an AIRD. Evaluation of the risk of infection in individual patients needs to be done on a case-by-case basis, according to their disease activity and regimen of immunosuppressive therapy. Immunocompromised populations at special risk include patients with lymphoproliferative malignancies, organ transplant recipients, patients receiving systemic corticosteroids, and patients with AIDS.[18] The incidence of HZ is 10–20 times higher in patients infected with human immunodeficiency virus (HIV) than in age-matched HIV-negative participants, i.e. 29.4–51.5 per 1,000 person years.[74] Usually these patients do not qualify for vaccination, due to contraindications.

Symptoms

HZ: The pain experienced during a bout of shingles is primarily caused by inflammation of the sensory nerves. In a few cases, HZ can be subclinical or exceedingly mild in nature. HZ most commonly localises to the thoracic region followed by the cranial region. HZ can start with a headache, malaise of varying severity, fatigue, dysesthesia, pruritus and fever. These symptoms are usually followed by sensations of burning, itching, tingling and numbness. The symptoms may precede the HZ eruption. Diagnosis of HZ in the prodromal period can be extremely difficult. The diagnosis can be facilitated by the appearance of the rash and by questioning the patient about their clinical history. If the rash does not occur, it is very difficult to diagnose the disease because HZ presents symptoms similar to those of other diseases. The acute phase of HZ, as the virus reaches the dermis and epidermis, is characterised by inflammation and blistering of the skin, shown as unilateral and vesicular rash that lasts up to 4 weeks, most often accompanied by pain or discomfort. Usually the pain

disappears spontaneously within a few weeks. However, if the pain becomes chronic, we speak of a complication called PHN.

Herpes zoster ophthalmicus (HZO)[18 19]

In elderly patients shingles may appear more often in the face, and may be the cause of HZO. In ophthalmic zoster a symptom is the conjunctivitis that resolves within a week. Other symptoms are a redness with dilatation of the vessels and a red eye with the reduction of the corneal sensitivity. These symptoms can cause chronic ocular inflammation, loss of vision and debilitating pain.[75] The risk of eye infection is independent of the severity of the initial symptoms and the age of the patient. The ophthalmological complications usually develop no earlier than the second week after the development of the rash.

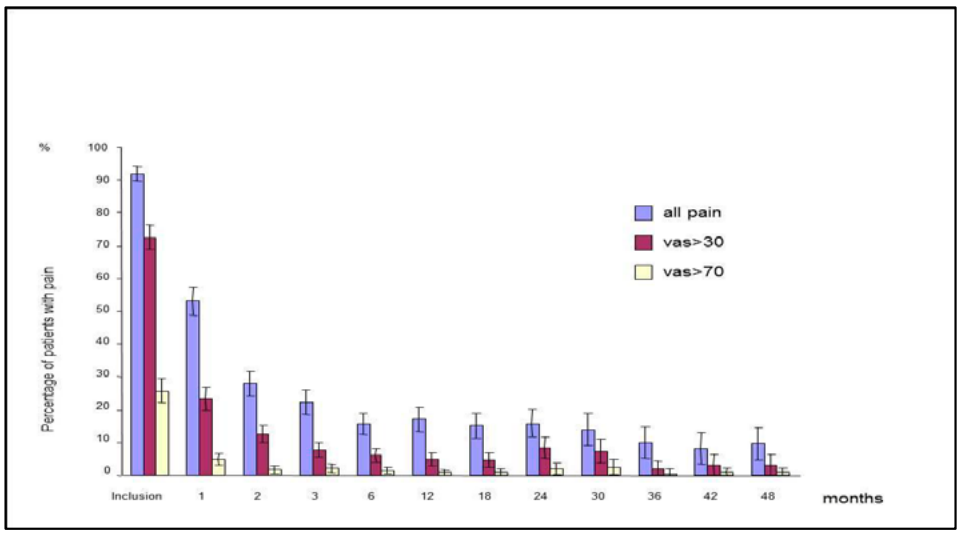
Complications

The complication postherpetic neuralgia (PHN)

PHN is the most common debilitating complication of HZ. In a long term prospective cohort study, Van Wijck et al., 2006, studied the long term natural history of zoster associated pain up to 48 months after the occurrence of HZ in patients >50 years in the primary care setting.[20] At three months, 22% of the patients reported pain, 8% significant pain (VAS>30) and 2% severe pain (VAS>70). At one year the proportion of patients reporting any pain gradually decreased to 17%, and to 16% at year two. At year three and four 10% of the patients still reported pain, of which 1-4% had long lasting severe pain (figure 13).

Two processes play a role in this phenomenon: sensitization and deafferentation. Sensitization is when the nerves involved in the long-lasting intense pain become more sensitive to pain stimuli. The accompanying clinical symptom is hyperalgesia. Central sensitization is linked to an increasingly stronger response of the neurons in the dorsal horn to the continuous stimulus of the nociceptive C-fibres. The area where the pain is felt increases in size. While sensitization is considered a normal physiological process, deafferentiation is not. Deafferentiation means the loss of neurons and can be caused by the replication of the virus in the cell and/or subsequent inflammatory reaction. The swelling that accompanies the inflammation can pinch the sensory ganglion in the foramen intervertebrale and result in ischemia and nerve tissue damage (see figure 3, section C.1).

Figure 13: Incidence of pain over time after onset of HZ.[20] Note: pain scores are with treatment.



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Deafferentiation is associated with neuropathic pain. Because the normal input in the spinal cord is absent, pathological connections arise in the dorsal horn between the areas for pain and those for touch. Tactile impulses are felt as pain (allodynia) and a constant burning pain arises. Even a light touch, like that of clothing or the bedclothes at night, can become unbearable. Pain is one of the main symptoms of PHN and has, both for HZ and PHN, a strong impact on perceived quality of life. High levels of pain (score 8–10) on average and at worst were reported by greater proportions of patients with PHN than with HZ.[76] Pain and anxiety are the dimensions of EQ-5D that are most affected by HZ. HZ and PHN have a negative impact on the physical, psychological, functional and social status of patients. A strong relationship between pain and activities of daily living (ADL) emerges from the literature. The Zoster Quality of Life (ZQOL) study on the burden of PHN, performed in the UK, demonstrated that PHN has a significant impact on Health Related Quality of Life (HRQoL).[24] Accordingly, scores for SF-36 and EQ-5D indicated significant deficits in HRQoL among PHN patients compared to age-matched norms ($p<0.05$) and patients reported being dissatisfied with the perceived efficacy of therapies received for the management of PHN. The inadequate relief provided by PHN therapies available in the UK is associated with a significant burden among PHN patients in terms of pain severity and deficits in HRQOL which may persist for years.[24]

Other complications

There is a risk of viral dissemination with immune disorders. This can be life-threatening. Rare, but serious complications of HZ include encephalitis, pneumonitis, delayed contralateral hemiparesis (which is probably the result of VZV in the cerebral arteries and can appear weeks to months after the development of facial vesicles), and dysfunction of motor neurons (e.g. Bells paresis and the Ramsey Hunt syndrome).[75]

Hospitalisation due to HZ and PHN[18]

HZ infection and its complications, especially PHN are associated with high rates of health care utilization, for outpatient visits and prescription of medicinal products, but also leads to hospitalisations in several cases. European studies showed an average length of stay for HZ ranges from 8.1 days to 12.9 days. A higher hospitalisation rate is reported for female patients compared with male patients. Few data are available on hospitalisation and PHN. In the UK, 11% of hospitalised cases of HZ also had a diagnostic code for PHN. The case-fatality rate during hospitalisation is high in people aged above 80, reaching 7.2%. Data available from The Netherlands is reported by De Melker et al., 2006.[69] Both the annual number of hospital days and the average number of days per admission increases with increasing age, particularly from 70 years of age onwards.

Table 11: Hospitalisation rate for HZ per 100,000 for The Netherlands.[70]

Age groups (years)	Hospitalisation rate per 100,000*
50-54	1.2
55-59	1.3
60-64	1.4
65-69	2.1
70-74	2.8
75-79	4.5
80-84	5.9
85+	5.3

*Hospitalisation rate is per 100,000 and considers both main and side diagnosis for HZ, based on GP consultations.

Mortality

Data on HZ mortality are limited but tend to show that fatal cases are likely to be rare especially among immunocompetent, healthy people. HZ is rarely recorded as the cause of death in patients under the age of 65.

Age-specific mortality data is only available in the Netherlands; it shows a sharp increase after the age of 80.[77] According to CBS figures death attributable to HZ in 2012 amount to 21 (<70: 1 death; 70-80:4 deaths and >80 years 16 deaths).

C.2 Treatment

The objectives of treating HZ are to control acute pain, accelerate rash healing, minimize complications, and reduce the risk of PHN or other late appearing sequelae. An additional objective, important for immunosuppressed patients, is to reduce the risk of cutaneous and visceral dissemination of the VZV.

Treatment of the viral infection[18] [19]

In the acute phase, systemic antiviral therapy is the mainstay treatment of HZ across Europe and outside Europe. The international guidelines on HZ treatment of Dworkin et al., 2007[21] apply the following criteria for systemic antiviral therapy for immunocompetent patients with HZ: (1) 50 years of age; (2) have moderate or severe pain; (3) have moderate or severe rash; or (4) have nontruncal involvement. In patients who have a low risk for complications of HZ—for example, those who are younger with mild acute pain and rash and truncal involvement—the potential benefits of treatment are unknown but may be meaningful because such patients can still develop PHN. The antiviral therapies acyclovir, famciclovir, and valacyclovir are approved by the FDA and EMA for the treatment of HZ. These treatments reduce the duration of viral shedding and lesion formation, and therefore decrease the severity and duration of acute pain from zoster and the risk for progression to PHN. Acyclovir, famciclovir, and valacyclovir are all exceptionally safe, which contributes to a favourable balance of potential benefit versus risk, although dose adjustment may be necessary in patients with decreased renal function. It is, therefore, recommended that antiviral therapy be considered even for patients whose risk of developing PHN and other complications of HZ is likely to be low. The main challenge of antiviral therapy is that, to be effective, treatment needs to be initiated within 72 hours of the onset of rash. In a few cases, e.g. delay of the medical visit, the presence of new vesicles or complications, therapy is started more than 72 hours after the onset of acute symptoms. In patients presenting >72 hours after rash onset, the potential benefits of initiating antiviral therapy are unknown but might be meaningful, given the minimal risks of treatment with acyclovir, famciclovir, and valacyclovir. Advanced age and severe pain (which are potent risk factors for PHN) are additional factors that can prompt consideration of initiating antiviral therapy >72 hours after rash onset. In patients who still have new vesicles forming or who have cutaneous, motor, neurologic, or ocular complications after 7 days of antiviral therapy, close monitoring is recommended and also extension of the duration of antiviral therapy for >7 days.

The international guidelines conclude that although the results of each of the antiviral clinical trials taken singly can be challenged, the preponderance of the findings provides strong support for the use of antiviral therapy to hasten resolution of the acute phase.

The guidelines in The Netherlands (Dutch College of General Practitioners)[25] for the treatment of (severe symptoms of) HZ/PHN recommend as well the use of an oral antiviral agent (acyclovir, famciclovir and valacyclovir), for immunocompetent patients >50 years and patients with HZ in the head/neck/face area within 48 to 72 hours after onset of the eruption. The clinical relevance of the effect of antiviral therapy on resolution of the skin lesions and the duration of acute pain, is judged as minimal. For immunosuppressed patients, hospitalization with intravenous antiviral therapy is recommended to prevent viral dissemination.

Treatment of pain

HZ: The international guidelines[21] regard effective relief of acute pain as a necessary treatment goal. Pain should be assessed and treated promptly, and next to antiviral therapy, the choice of treatment approach depends on the patient's pain severity, underlying conditions, and on prior response to specific medications.

The principles of state-of-the art pain management, such as the use of standardized pain measures, scheduled analgesia, and consistent and frequent follow-up to adjust dosing to the needs of the patient, should be applied to the management of pain in patients with HZ. It is important to recognize that HZ pain changes over time and can become more severe as the acute infection progresses. Patients with mild to moderate pain may be managed with high dose acetaminophen (up to 4 g/day) or an NSAID combined with a gastro-protective agent, alone, in combination with a weak opioid analgesic (e.g. codeine, tramadol)., or with strong opioids (e.g. oxycodone, morphine). One has to consider that weak opioids give a very individual response because of existing polymorphism. These commonly used medications, however, have not been studied for the treatment of HZ and oxycodone and morphine have been proven effective only in two published studies in PHN.[78] Pain medication should be given at regular interval 'round the clock' and not as needed. For pain that is moderate to severe in intensity, which is often accompanied by disturbed sleep, treatment with a strong opioid analgesic (e.g. oxycodone or morphine) is recommended on the basis of the consistent efficacy of this class of medications in patients with inflammatory and neuropathic pain. If moderate to severe pain in patients with HZ has not responded rapidly to treatment with an opioid analgesic, the prompt addition of one of the following 3 classes of oral medications in combination with the opioid analgesic should be considered, even though few studies have examined whether the risk of PHN is reduced by such treatment: (1) gabapentin or pregabalin; (2) TCAs, especially nortriptyline; or (3) corticosteroids (e.g. prednisone), if there are no contraindications. For those patients with moderate or severe pain who are unable to tolerate an opioid analgesic, treatment with these 3 classes of medications, alone and in combination, can be considered.

PHN: PHN can be treated as any peripheral neuropathic pain syndrome. For the treatment of neuropathic pain in The Netherlands[26], the following pharmacotherapeutic treatment options are available:

- Antidepressants (such as nortriptyline, SSRIs, duloxetine)
- Anti-epileptics (including carbamazepine, phenytoin, gabapentin, pregabalin)
- Opioids
- Topical treatment such as capsaicin cream, capsaicin plaster, lidocaine 5%)

For patients with pain that is inadequately controlled by the above mentioned treatment options, the following medical treatment options are available:

- Referral to a pain specialist or pain centre is recommended to evaluate eligibility for neural blockade or neuromodulation with transcutaneous nerve stimulation, nerve root stimulation or spinal cord stimulation. Although long-term benefits of neural blockade in HZ have not been established, these procedures can reduce severe acute pain, and their risk-benefit ratio is therefore likely to be favourable.
- Patients with the most severe lesions and pain may benefit from hospitalisation and administration of epidural analgesics.

In conclusion: Despite antiviral and pain treatment of HZ, PHN is not prevented. Once established, PHN is a persistent and difficult-to-treat pain syndrome with a significant burden in terms of pain severity and deficits in health related quality of life which may persist for years.[24] [79]

C.3 Prevention

Prevention of HZ and PHN by medical-pharmaceutical treatment options

It is concluded that, nor HZ, nor PHN can be prevented by any available medical-pharmaceutical therapy.

Prevention through vaccination

Due to the lack of preventive measures for HZ apart from the HZ vaccine, there is no joint guideline for the EU

dealing with the prevention of HZ, but some national guidelines exist worldwide. In 2008, the Advisory Committee on Immunization Practices (ACIP) in the US recommended the use of a live attenuated vaccine in adults aged 60 years and above for the prevention of HZ and its sequelae.[60] This recommendation is still maintained after evaluation of the vaccination program in 2014.[80] In 2010 the National Advisory Committee on Immunization (NACI), that provides the Public Health Agency of Canada with public health advice relating to immunization, recommends HZ vaccination for the prevention of HZ and its complications in adults aged 60 years and above without contraindications.[81] This recommendation is reinforced in the consensus statement from the Canadian Pain Society in 2015.[82]

In the United Kingdom, the national Green Book keeps health professionals and immunisation practitioners up to date with developments and latest information on vaccines and vaccination procedures, for vaccine preventable infectious diseases. Since 2013, the Green Book[53] recommends a routinely vaccination programme for HZ to adults aged 70 and adults aged 79 as part of the catch-up campaign.[54]

Herpes zoster vaccine[18 19 83]

The first live attenuated injectable herpes zoster vaccine (HZ vaccine) available worldwide is Zostavax (manufacturer Sanofi Pasteur MSD). HZ vaccine is a lyophilised preparation of live, attenuated vaccine containing VZV (Oka/Merck strain). Each dose (0.65 ml) contains not less than 19,400 plaque forming units (PFU) of VZV. HZ vaccine contains the same strain as used in vaccines to prevent varicella (the primary infection of VZV) but at a higher potency. HZ vaccine was first authorised in Australia on 2 May 2006. The vaccine was authorised in the EU on 19 May 2006 and in the US on 25 May 2006 and the first launch worldwide was in the US in June 2006. In Europe, market authorization is granted for the refrigerated formulation whereas in the clinical studies the frozen formulation was mostly used.

HZ vaccine is indicated for prevention of HZ and HZ-related PHN. It is indicated for immunisation of adults aged 50 years and above. The groups not eligible for vaccination are those:

- with hypersensitivity to the active substance, or to any of the excipients or trace residuals (e.g. neomycin)
- with primary and acquired immunodeficiency states due to conditions such as acute and chronic leukaemia's; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS; cellular immune deficiencies
- undergoing immunosuppressive therapy (including high-dose corticosteroids); however, HZ vaccine is not contraindicated for individuals receiving topical or inhaled corticosteroids, or low-dose systemic corticosteroids, or patients who are receiving corticosteroids as replacement therapy (e.g. for adrenal insufficiency) with active untreated tuberculosis
- who are pregnant.

HZ vaccine is available as a powder and solvent to be made up into a suspension for injection. It is given as a single dose of 0.65 ml injected subcutaneously in the deltoid region of the upper arm.

Available evidence[18 19 34 35 36 36 37]

The safety and clinical effectiveness of HZ vaccine has been investigated in several clinical studies. The first pivotal randomised controlled trial (RCT) is the Shingles Prevention Study (SPS)[34], which enrolled 38,546 participants aged 60 years or older (intervention group: 19,270, placebo group: 19,276 participants; intention to treat population). A sub study of the SPS (Adverse Event Substudy)[35] involving 6,616 participants within the SPS cohort (intervention group 3,345 participants and placebo group 3,271 participants) has also been conducted for further evaluation of adverse events. Mean follow-up of the SPS is 3.1 years. The second RCT is the Zostavax Efficacy and Safety Trial (ZEST)[36], which included 22,439 participants aged 50-59 years

(intervention group: 11,211 participants, placebo group: 11,228 participants; intention to treat population). Mean follow-up was 1.3 years. The primary efficacy outcome of the SPS is vaccine efficacy for the burden of illness (BOI), a composite endpoint affected by the incidence, severity and duration of the associated pain and discomfort. The primary outcome of the ZEST is incidence of HZ. Secondary endpoints in the SPS is the incidence of PHN and for the ZEST antibody titre and safety. The incidence of PHN is not studied in the ZEST study for subjects aged 50-59 years, due to the epidemiological features of PHN which occur more frequently after the age of 60 or even 70. Three studies reported real life data on an HZ vaccination programme conducted in the USA.[84] [85] [86]

Efficacy and effectiveness

The SPS study shows that, compared with placebo, a single dose of HZ vaccine effectively decreases the incidence of HZ and PHN in immunocompetent adults aged 60 years and above. The HZ vaccine reduced the incidence of HZ in those aged 60 years and above and in those aged 70 years and above by 51.3% and 38% respectively, and the incidence of PHN by 66.5% and 66.8% respectively.[34] The BOI in those aged 60 years and over and in those aged 70 years was reduced by 61.1% and 55.4% respectively. The ZEST study shows that, compared with placebo, a single dose of HZ vaccine effectively decreases the incidence of HZ in immuno-competent adults aged 50 - 59 years. The HZ vaccine reduced the incidence of HZ by 69.8% and the BOI by 73%.[36] Vaccination with HZ vaccine did not reduce mortality and hospitalisation rates due to HZ/PHN. Also, an improvement of HRQOL in vaccinees who developed HZ cannot be demonstrated. There is insufficient evidence to determine whether pain and activities of daily living are influenced by HZ vaccine. Due to limitations of the methodology used, the effect of HZ vaccine on activities of daily living and pain reduction is not clear.
RCT results on the ability of HZ vaccine to prevent HZ have been confirmed in the real life studies.[84] [85] [86] According to a Cochrane review, 2012[87] the number needed to treat to benefit (NNTB) is 50. However, this is an estimate for the overall group. Information about age specificity is not available.

Safety[83]

In immunocompetent participants aged 50 years and above, a single dose of HZ vaccine has a low-risk safety profile. The most frequent adverse reactions, reported in ≥1% of participants vaccinated with HZ vaccine, were headache and injection-site reactions. In the clinical studies, the overall incidence of vaccine-related injection-site adverse reactions was significantly greater for participants vaccinated with HZ vaccine (frozen formulation) versus participants who received placebo (48% versus 17% in SPS Substudy[35] and 63.9% versus 14.4% in the ZEST[36]).
Within the SPS, side effects were more frequent in younger (60 to 69 years) than in older (70 years and above) participants. Vaccine-related systemic adverse effects in those aged ≥60 years were more frequent in the vaccinated group (RR 1.29, 95% CI: 1.05 to 1.57; 1.93% versus 1.29%; p=0.038), number needed to treat to harm (NNTH) is 100).[35] In the subgroup of ≥70 years, no statistical significant difference was found (1.66% versus 1.78%; p=0.55).[35] The number and percentage of participants reporting any systemic clinical adverse experience were greater in the 50 to 59 year group (ZEST)[36] as compared to the ≥ 60 year group (SPS).[35]
Table 12 presents vaccine-related injection-site and systemic adverse reactions reported at a significantly greater incidence in the vaccine group versus the placebo group in the Adverse Event Monitoring Substudy.[35] Table 12 also includes additional adverse events which have been reported spontaneously through post-marketing surveillance.[33] Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "*not known*". They are ranked under headings of frequency using the following convention: [Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000)].

Table 12: Adverse events of the HZ vaccine reported in the Summary of Product Characteristics.[33 35]

MedDRA System Organ Class	Adverse reactions	Frequency
Infections and infestations	Varicella Herpes zoster (vaccine strain)	Very rare Very rare[1]
Blood and lymphatic system disorders	Lymphadenopathy (cervical, axillary)	Not known**
Immune system disorders	Hypersensitivity reactions including anaphylactic reactions	Not known**
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Not known**
Skin and subcutaneous tissue disorders	Rash	Not known**
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia Pain in extremity	Not known** Common
General disorders and administration site conditions	Erythema†*, Pain/tenderness†*, Swelling†*, Pruritus†,Haematoma†, Warmth†, Induration† Rash†, Urticaria†, Pyrexia	Very common Common Not known**

*Several adverse reactions were solicited (within 5 days post-vaccination).

** Post marketing adverse events (frequency cannot be estimated from the available data).

† Injection-site adverse reactions

[1] This adverse reaction was identified through post-marketing surveillance but not observed in the clinical development program. The frequency category was estimated from a statistical calculation based on zero cases out of the total number of patients exposed to HZ vaccine in the clinical development program (n > 57,000).

Outcomes of assessments of HZ vaccine by health authorities

In Europe, assessment reports of the HZ vaccine are published by four independent, European health authority bodies. The assessment of the UK's Joint Committee on Vaccination and Immunisation (JCVI) in 2010 has been discussed extensively in section 2.1 of this report.[38] In 2013, the French health authorities ('Haute Conseil de la Santé Publique, HCSP)[39] assessed the HZ vaccine and recommended to implement vaccination with the HZ vaccine for adults aged 65 to 74 years and to perform a catch-up programme for adults aged 75 to 79 years. It took until recently, June 2015, before the French Ministry of Health decided to provide reimbursement for individual vaccination. Because the French situation of reimbursement is very recent and no experience exists with the implementation of HZ vaccination, as is the case in the UK, we didn't discuss the French assessment in more detail in this section. In 2013, the European HTA Group ´EUnetHTA´ (a voluntarily cooperation of European Health Authorities) assessed prevention with HZ vaccine for individuals ≥50 years of age.[18] In 2014, the National Health Care Institute (Dutch: Zorginstituut Nederland, ZINL) assessed a subgroup of 70-79 years of age.[19] The ZINL assessment is discussed in more detail because it refers to The Netherlands. Because ZINL used the assessment of EUnetHTA for their own assessment, the EUnetHTA assessment is discussed in more detail as well. Of both assessments the discussion and conclusion

Discussion by EUnetHTA[18]

"Both clinical studies discussed in this assessment (SPS and ZEST) are well-designed RCTs. In both trials the total number of participants in the two cohorts was sufficient to assess possible difference in the incidence of HZ. However, because the incidence of PHN is lower, the number of confirmed cases of PHN in the studies was low. Further, because of its particularly low incidence in participants aged 50-59 years old, the incidence of PHN was not studied in this age group. Other relevant limitations of the results are:

· After initial registration, the formulation of HZ vaccine was changed from a frozen one to a refrigerated one. Although the bridging study, as required by the EMA, showed comparable VZV antibody geometric mean titres

in the two formulations, the effect of the refrigerated formulation on relevant outcomes, such as prevention of HZ or PHN, has not been studied.
· Individuals with compromised immunity were excluded from the studies (contraindication). There is limited information about the effectiveness of HZ vaccine in this group, who may need a preventive vaccine the most.
· People who have been vaccinated can later become immunocompromised, as a result of senescence, disease or medication. It is not clear whether such people will be more susceptible to reactivation of VZV.
· The primary endpoint in SPS (vaccine efficacy for BOI) is a composite endpoint. Composite endpoints are multifactorial, difficult to interpret and their incorrect interpretation may result in an overestimation of the effects of an intervention. It is also possible that the calculated effect results from multiplying artefacts. Analysis of the individual parameters separately is a partial solution to this problem.
· Pain control and improved quality of life are important for affected patients. The methods of pain assessment in the clinical trials are questionable. In addition to the methodological limitations of the studies, the clinical relevance of the measured outcome parameters is not certain.
· The oldest age group is most vulnerable, but the oldest elderly (participants aged 80 years of older), was not a prespecified subgroup in the studies. The posthoc analysis of this relatively small subgroup entails uncertainties.
Long-term data about safety and efficacy after 10 years is lacking. Therefore, the relevance of an eventual revaccination cannot be assessed within the remit of this report."

Conclusion of the therapeutic value of the HZ vaccine according to EUnetHTA[18]
"HZ vaccine administered as a single dose in immunocompetent people aged 50 years or older is more effective in preventing HZ than is placebo. This incidence lowering effect decreases with increasing age. Beyond the prevention of HZ, there may be an effect on the prevention of PHN by HZ vaccine in certain age groups (70-79 years). More data are required to demonstrate this conclusively. No significant effect can be shown on mortality, hospitalisation rate and HRQL. Due to limitations of the methodology used, the effect of HZ vaccine on activities of daily living and pain reduction is not clear.
A single dose of HZ vaccine in immunocompetent people aged 50 years or older has a similar safety profile compared with placebo. Subgroup analysis showed that age is a risk factor for severe adverse events. Participants aged 80 years or older were at greatest risk. However, because this age group was not a predefined age stratum, further investigations are needed to determine the risk profile in the oldest elderly. People with compromised immunity are excluded from the clinical trials, so limited data about the efficacy of HZ vaccine in this group is available. Long-term data (beyond 10 years) about efficacy and safety is lacking. Therefore, the relevance of an eventual revaccination cannot be assessed within the remit of this report."
No further recommendation for implementation was provided to Ministries of Health in Europe.

Summary of the therapeutic value of the HZ vaccine according to ZINL[19]
"Beneficial effects: Vaccination of immunocompetent individuals aged 70 years and above with HZ vaccine leads to a reduced risk of developing HZ and the possible subsequent PHN. The beneficial effects of this vaccine are related to the ability of an individual to develop an immune response to the vaccination. Aging or an immunocompromised status may lead to an impaired immune response. Vaccine efficacy for the prevention of both diseases for individuals aged 70 years and above is overall 38% and 47% respectively, compared with placebo, with better results in the younger cohorts and worse in the elderly. There are no published data on the effect of the HZ vaccine on the pain caused by HZ in people aged 70 years and above. The HZ vaccine does not affect the quality of life of someone who has developed HZ. Although research is ongoing, no clinical studies have been published on the effects of this vaccine in people with impaired immunity.
Adverse effects: The most commonly reported side effects of the HZ vaccine are local reactions at the injection

site. Compared to placebo, these generally mild reactions, are more frequent following the administration of the vaccine. Of the people who received the vaccine, 1.66% has one or more serious side effects. This rate is not significantly different compared to the control group (1.78%).
Experience: HZ vaccine is registered in Europe since 2006. There is plenty of experience with this vaccine in adults aged 70 years and above.
Applicability: HZ vaccine is amongst others contraindicated in people with an impaired immune response due to illness or treatment that inhibits the immune system. This vaccine should not be administered simultaneously with the 23-valent pneumococcal polysaccharide vaccine, as this leads to a reduced immunogenicity of the HZ vaccine. Co-administration of inactivated influenza vaccine is possible, provided that the two are administered as separate injections and at different sites on the body. There are no data on the concomitant administration of other vaccines such as travellers vaccines.
Ease of use: HZ vaccine is injected subcutaneously only once. It is not known whether a booster injection is required, and if so, when."

Conclusion of the therapeutic value of the HZ vaccine according to ZINL[19]
"In the prevention of HZ and PHN in immunocompetent adults aged 70 years and above the HZ vaccine has therapeutic added value compared to placebo. The efficacy of the vaccine for the prevention of HZ and PHN is demonstrated. The probability of developing a serious side effect is not significantly different between those who have been immunized with the HZ vaccine compared to placebo. This vaccine does not affect someone's quality of life after HZ has developed. There are no data available on the effect of the HZ vaccine on the pain caused by HZ in people aged 70 years and above." Despite a recommendation for implementation by the ZINL, the Ministry of Health in The Netherlands has not decided up till now (July 2015).

<u>New development</u>
In May 2015, the results were published of a new HZ vaccine, currently under research. It is a recombinant subunit herpes zoster vaccine containing the vaccine antigen VZV glycoprotein E adjuvanted with $AS01_B$ (called HZ/su, GlaxoSmithKline Biologicals).[41 42] The problem with pure recombinant or synthetic antigens used in modern day vaccines is that they are generally far less immunogenic than older style live or killed whole organism vaccines. This has created a major need for improved and more powerful adjuvants for use in these vaccines.[88] VZV glycoprotein E was selected as a candidate vaccine antigen because it is essential for viral replication and cell-to-cell spread and is a primary target of VZV-specific immune responses. The adjuvant $AS01_B$ consists of monophosphoryl lipid A and QS21, a saponin compound, formulated with liposomes. The adjuvant activates antigen-specific CD4+ T cells and antibody.4 Cell-mediated immunity, especially production of CD4+ T cells that target VZV, is associated with protection from HZ, whereas antibody protects against varicella. $AS01_B$ has been used in studies of vaccines against malaria, hepatitis B, human immunodeficiency virus (HIV), and tuberculosis4, however it is currently not a licensed adjuvant.
Recombinant subunit vaccines are an alternative to live-attenuated vaccines and may also be suitable for persons with immunosuppression because the risk of disease resulting from replication of the vaccine virus is prevented.[43] Previous phase 1–2 clinical trials that were conducted in older adults and in persons with immunosuppression showed that HZ/su had a clinically acceptable safety profile and elicited a robust immune response that persisted vaccine efficacy similar among all age groups. Since the HZ/su vaccine contains only a single virus protein and therefore cannot replicate, it will probably be safer in such patients, although it has to be proven whether the HZ/su vaccine will elicit a sufficiently protective immune response.

Available evidence[41]

A randomized, placebo-controlled, phase 3 study was conducted to evaluate the efficacy and safety of HZ/su in older adults (≥50 years of age), stratified according to age group (50 to 59, 60 to 69, and ≥70 years). Participants received two intramuscular doses of the vaccine or placebo 2 months apart. The primary objective was to assess the efficacy of the vaccine, as compared with placebo, in reducing the risk of HZ in older adults. A total of 8,926 participants were assigned to the reactogenicity subgroup (4.460 in the HZ/su group and 4,466 in the placebo group).

Efficacy[41]

Most participants received two doses of the study vaccines (95.6% of HZ/su recipients and 96.4% of placebo recipients). In this phase 3 efficacy trial of a subunit vaccine against HZ, two doses of HZ/su administered 2 months apart had a vaccine efficacy of 97.2%, as compared with placebo, in reducing the risk of HZ in adults 50 years of age or older. The vaccine efficacy was similar among the three age groups (95% confidence interval [CI], 93.7 to 99.0; P<0.001).

Safety[41]

To date, no safety concerns have been identified, although solicited injection site and systemic reactions were more frequent in the HZ/su group. In the reactogenicity subgroup, solicited or unsolicited symptoms within 7 days after vaccination were reported in 84.4% of participants in the HZ/su group and 37.8% in the placebo group. Most symptoms were of mild-to-moderate intensity, but 17.0% of HZ/su recipients and 3.2% of placebo recipients reported symptoms that prevented normal everyday activities (grade 3). Solicited systemic reactions occurred in 66.1% of HZ/su recipients (grade 3 in 11.4%) and 29.5% of placebo recipients (grade 3 in 2.4%).The overall frequencies of solicited reactions were similar after each dose, but grade 3 solicited systemic reactions were more frequent after the second dose (8.5%; 95% CI, 7.7 to 9.4) than after the first dose (5.9%; 95% CI, 5.2 to 6.6). Previous studies suggest that the antigen and the adjuvant both contribute to the difference in solicited injection-site and systemic reactions.[44]

Comparison of HZ vaccine and HZ/su

The recombinant subunit vaccine seems promising because of the sustained high efficacy among all age groups and its supposed suitability for immunosuppressed individuals.[43]

However, in the phase 3 study immunosuppressed individuals were excluded. Side effects were in particular provoked by the reactogenicity of HZ/su vaccine (2.2 times more solicited systemic reactions than placebo), whereas in the HZ vaccine (live attenuated vaccine) study the rates of systemic adverse events were similar compared to placebo.[42] The benefits flowing from adjuvant incorporation into any vaccine formulation have to be balanced with the risk of adverse reactions. Exacerbation or triggering of immune-mediated diseases in susceptible persons is a hypothetical concern for vaccines containing new adjuvants such as $AS01_B$ because of their immunostimulatory effects. Adjuvants have recently been implicated in the new syndrome named 'ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants', which describes an umbrella of clinical conditions including post-vaccination adverse reactions.[45] The administration of two doses, two months, apart may lead to non-compliance, and thereby reduced health gain.

Table 2: Comparison of HZ vaccine with HZ/su vaccine.

	HZ vaccine (Zostavax)[18 19 33 34 35 36]	HZ/su vaccine[41 42]
Marketing Authorisation (MA)	May 2006	No MA, currently under research
Type of vaccine	Live attenuated vaccine containing VZV	Recombinant subunit vaccine: HZ/su vaccine containing a single VZV glycoprotein in an $AS01_B$ adjuvant system
Indication	Prevention of HZ and HZ-related PHN of people aged 50 years and above	Not known yet.
Contraindications	Hypersensitivity Primary/acquired immunodeficiency state Under immunosuppressive therapy (exceptions topical or inhaled or low-dose systemic corticosteroids or corticosteroids as replacement therapy Pregnancy	Not defined yet
Administration	A single dose parenteral intramuscular (i.m.) injection	A double dose, two months apart parenteral i.m. injection
Co-administration with influenza vaccine	Possible	Unknown
Co-administration with pneumococcal vaccine	Possible	Unknown
Study population	Immunocompetent population 38,546 aged ≥60 years 22,439 aged 50-59 years	Immunocompetent population 15,411 ≥50 years
Efficacy: **Prevention of HZ**	50-59 years: 69.8% ≥60 years and above 51.3% ≥70 years and above 38%	50-59 years 96.6% 60-69 years 97.4% ≥70 years and above 97.9%
Efficacy: **Prevention of PHN**	50-59 years: not measured ≥60 years and above 66.5% ≥70 years and above 66.8%	50-59 years not measured 60-69 years not measured ≥70 years and above not measured
Mortality	Comparable to placebo	Comparable to placebo
Total study population **Serious adverse events** **Substudy** **-Adverse events** **-Solicited systemic adverse events** **-Injection site reactions** **-Serious adverse events**	Measured after 42 days post-vaccination Comparable to placebo (1.4% vs. 1.4%) Adverse events substudy: 5 days post-vaccination 58% vs. 34% 25% vs. 24% 48% vs. 17% ≥60 years and above: 1.93% vs 1.29; p=0.038 ≥70 years and above: 1.66% vs 1.78%; p=0.55	Measured after 30 days Comparable to placebo (1.1% vs 1.3%) Reactogenicity study; 7 days post-vaccination 84% vs. 38% 66% vs. 30% 82% versus 12% Not reported Not reported

C.4 Cost-effectiveness of prevention

Numerous cost-effectiveness evaluations have been carried out internationally, which have been evaluated in a recent review (De Boer et al., 2014).[46] Two other cost-effectiveness evaluations are performed for The Netherlands by the RIVM (Van Lier et al., 2010)[47] respectively University of Groningen (De Boer et al., 2013)[48].

Of both health authority bodies that assessed the HZ vaccine on efficacy and safety, i.e. EUnetHTA (2013) and ZINL (2014), only ZINL has addressed the cost-effectiveness of the HZ vaccine.[19]

ZINL cost-effectiveness assessment for individual HZ vaccination[19]

As part of the assessment of HZ vaccination in The Netherlands (2014), ZINL reported incremental cost-effectiveness ratios (ICERs) for the total population of ≥70 years of age of €37,816 per QALY gained, €4,494 per prevented case of HZ and €16,243 per prevented case of postherpetic neuralgia (PHN). The outcomes are sensitive to incidence and length of PHN and utility scores of serious pain in PHN. If it is assumed that the incidence of PHN is higher and vaccination decreases this incidence, the ICER decreases to €6,888 per QALY gained. If it is assumed that pain is less serious in the most severe pain cases of PHN, the ICER increases to €68,634 per QALY gained. The ICER varies among age categories: €80,667 per QALY gained for the population ≥80 years of age and €26,844 per QALY gained for the population 70-79 years of age. As usual, costs of administration and price of the vaccine influence the cost-effectiveness. ZINL concluded that the cost-effectiveness is of sufficient methodological quality.

RIVM cost-effectiveness assessment for programmatic HZ vaccination[47]

Already in 2010, the RIVM performed an assessment of the potential effects and cost-effectiveness of programmatic HZ vaccination of elderly in the Netherlands according to a framework that was developed to support evidence based decision making regarding inclusion of new vaccines in the Dutch National Immunization Program. The cost-effectiveness analysis was performed from a societal perspective, using a Markov-cohort-model. Simultaneous vaccination with influenza was assumed. The RIVM reported that the combination of waning immunity after vaccination and a reduced efficacy of vaccination at high ages, the most optimal cost-effectiveness ratio (€21.716 per QALY gained) for HZ vaccination in the Netherlands was found for 70-year olds. This estimated ratio is just above the socially accepted threshold in the Netherlands of €20.000 per QALY gained. If additional reduction of postherpetic neuralgia was included, the cost-effectiveness ratio improved (~€10.000 per QALY gained) but uncertainty for this scenario is high. The RIVM concluded that vaccination against HZ at the age of 70 years seems marginally cost-effective in the Netherlands. Due to limited vaccine efficacy a considerable part of the disease burden caused by HZ will remain, even with optimal acceptance of programmatic vaccination.

University of Groningen cost-effectiveness assessment for cohort HZ vaccination[48]

In 2013, the University of Groningen estimated the ICER of vaccination of the elderly against HZ versus no such vaccination in The Netherlands. A cohort model was developed to compare the costs and effects in a vaccinated and a non-vaccinated age- and gender-stratified cohort of immune-competent elderly. Vaccination age was varied from 60 to 75 years. Data from published literature such as the pivotal HZ vaccine study (SPS) were used for transition probabilities. The study was performed from the societal as well as the health care payer's perspective. In the base case, the authors estimated that vaccination of a cohort of 100,000 60-year-olds would prevent 4,136 cases of HZ, 305 cases of PHN resulting in a QALY-gain of 209. From the societal perspective, a total of €1.9 million was saved and the ICER was €35,555 per QALY gained when a vaccine price of €87 was used. Vaccination of women resulted in a lower ICER than vaccination of men (€33,258 vs. € 40,984 per QALY gained). The vaccination age with the most favourable ICER was 70 years (€29,664 per QALY gained). Parameters with a major impact on the ICER were the vaccine price and HZ incidence rates. In addition, the model was sensitive to utility of mild pain, vaccine efficacy at the moment of uptake and the duration of protection induced by the vaccine. It was concluded that vaccination against HZ might be cost-effective for ages ranging from 60 to 75 when a threshold of €50.000 per QALY gained would be used, at €20,000 per QALY this might not be the case. Additional information on the duration of vaccine-protection is needed to further optimise cost-effectiveness estimations.

Review of cost-effectiveness studies[46]

In this review, the available literature on cost-effectiveness of HZ vaccination is summarised and critical parameters for cost-effectiveness results are discussed. A search in PubMed and EMBASE was performed to identify full cost-effectiveness studies published before April 2013. Fourteen cost-effectiveness studies were included, all performed in western countries. All studies evaluated cost-effectiveness among elderly ≥ 50 years and used costs per QALY gained as primary outcome. The vast majority of studies showed vaccination of 60 to 75-year-old individuals to be cost-effective, when duration of vaccine efficacy was longer than 10 years. Duration of vaccine efficacy, vaccine price, HZ incidence and discount rates were influential to the ICER. The authors conclude that HZ vaccination may be a worthwhile intervention from a cost-effectiveness point of view. However, more extensive reporting on methodology and more detailed results of sensitivity analyses would be desirable to address uncertainty and to guarantee optimal comparability between studies, for example regarding model structure, discounting, vaccine characteristics and loss of quality of life due to HZ and PHN.

Comparison with cost-effectiveness outcomes of other prevention programmes

The RIVM integrates the cost-effectiveness evaluation of preventive programmes in The Netherlands as part of it 4-yearly reporting about the health status of the population in The Netherlands (Future Health Report; Dutch: Volksgezondheid Toekomst Verkenning, VTV)[49] to the Ministry of Health, Welfare and Sports. The reported cost-effectiveness ratios for several prevention programmes are compared in table 3. Although other preventive programmes, like cervical and colon cancer screening, may be more cost-effective (€9,000, respectively <€20,000 per QALY gained)[49], the cost-effectiveness of the shingles vaccination programme compares well to the recently introduced HPV vaccination programme for 12-year old-girls (€18,400 - €30,000 per QALY gained) as well to the influenza vaccination programme (>€20,000 per QALY gained)[50].

Table 3: Cost-effectiveness ratios for prevention programmes in The Netherlands.

Prevention programme	Cost-effectiveness (costs per QALY gained)	Remarks
HPV vaccination in 12-year old girls[49]	€18,400 - €30,000	If a booster vaccination would be required, the cost-effectiveness ratio would increase with € 5,000 per QALY
Meningococcal catch-up of children aged 1-18 years[49]	€13,200-€17,000	A single catch-up campaign
Influenza vaccination of elderly aged ≥ 60 years[89]	>€20,000	The initial cost-effectiveness in 2007 was €15,500 Currently, the HC estimates >€20,000 (still to be calculated)
Pneumococcal vaccination of children aged >5 years[49]	€113,891 (PCV-7) € 52,947 (PCV-10) € 50,042 (PCV-13)	In case of dose-reduction: €113,891 (PCV-7) In case of dose-reduction: € 37,891 (PCV-10) In case of dose-reduction: € 35,743 (PCV-13)
Breast cancer screening (every two years) of women aged 50-70 years[49]	< €2,000-€5,000	
Colon cancer screening of elderly aged 50-70 years[49]	<€20,000	
Cervical carcinoma screening (every 5 years) of women aged 30-50 years[49]	€9,000	This represents the adjusted campaign; the cost-effectiveness of the initial campaign was €15,500

Declaration of interest

For this purpose Europe-ExPro makes use of the International Committee of Medical Journal Editors (ICMJE) form for disclosure of potential conflicts of interest (http://www.icmje.org/conflicts-of-interest/).

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Dr. A. van Wijck reports an unrestricted research grant from Sanofi Pasteur MSD outside the submitted work.

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