Kosteneffectiviteit van vaccinatie tegen windpokken bij kinderen en tegen zona bij ouderen in België

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Federaal Kenniscentrum voor de Gezondheidszorg
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VOORWOORD

Vaccins tegen windpokken (Varicella) zijn al meer dan twintig jaar op de markt, maar tot hiertoe was de aanbeveling van de Hoge Gezondheidsraad om het vaccin niet aan het vaccinatieschema voor zuigelingen en kinderen toe te voegen. Er bleven immers teveel vragen rond de geboden bescherming en vooral de duur ervan. Bovenden vreesde men een toename van het aantal gevallen van windpokken bij oudere kinderen en van zona bij volwassenen, vermits beide aandoeningen door hetzelfde virus worden veroorzaakt. Toch heeft men in sommige landen geoordeeld dat de risico's niet opwegen tegen de voordelen. Zo werd het in 1994 opgenomen in de vaccinatieschema's in de Verenigde Staten, en in 2004 in Duitsland.

In ons land adviseerde de Hoge Gezondheidsraad haar negatieve advies opnieuw in vraag te stellen eens de resultaten van het gecombineerde vaccin (mazelen, rode hond, bof en windpokken) zouden gekend zijn. Intussen heeft men hierover cijfers, en kent men ook beter de doeltreffendheid van het windpokken-vaccin. Bovendien is er nu ook een vaccin tegen zona (Herpes zoster) ontwikkeld en goedgekeurd.

Redenen genoeg dus om een studie te wijden aan de mogelijke impact van deze vaccins. Hoewel het om twee verschillende vaccins gaat, tegen twee verschillende manifestaties van hetzelfde virus, kan men effecten alleen in hun samenhang zinvol bestuderen. Dit maakte de studie methodologisch bijzonder uitdagend. Dank zij een intussen beproefde samenwerking met de onderzoekers van de Universiteit Antwerpen zijn we verheugd u vandaag deze baanbrekende analyse te kunnen aanreiken. Minder verheugend is dat ook vandaag nog grote onzekerheid blijft over de netto impact van de mogelijke vaccinatiestrategieën, iets wat de uiteindelijke beleidskeuze er niet gemakkelijker op zal maken.

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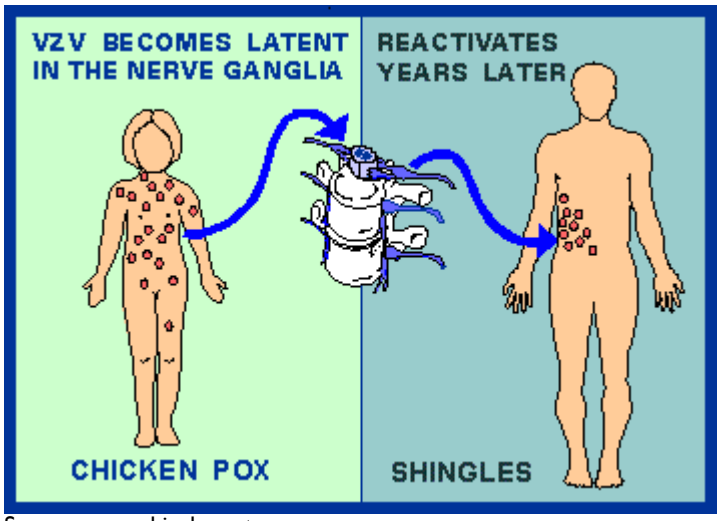
Samenvatting

INTRODUCTIE

Windpokken (varicella) is een gemakkelijk overdraagbare infectie veroorzaakt door het varicella zoster virus (VZV). In afwezigheid van vaccinatie, worden windpokken vooral gezien bij jonge kinderen. Ongeveer een op 200 kinderen met windpokken wordt gehospitaliseerd. Na het doormaken van windpokken blijft het virus latent aanwezig in het lichaam. Tot 20% van deze personen kunnen het virus terug zien verschijnen onder de vorm van zona (herpes zoster), dikwijls bij een verzwakking van het afweersysteem. Dit wordt geïllustreerd in onderstaande figuur.



Source: www.shingles.net.au

Het doel van deze studie was de kosteneffectiviteit te evalueren van twee vaccinatie opties: (1) vaccinatie tegen windpokken bij kinderen en (2) booster vaccinatie tegen zona bij volwassenen van 60 jaar en ouder. Ook het mogelijke effect van vaccinatie programma's tegen windpokken op de epidemiologie van zona wordt bekeken, met en zonder booster vaccinatie tegen zona.

Elke samenvatting hieronder bestaat uit een sectie introductie, doelstelling, methode, resultaten, discussie en conclusie.

VACCINATIE TEGEN WINDPOKKEN BIJ KINDEREN

INTRODUCTIE

De vaccins - Op basis van levend afgezwakt VZV zijn vaccins ontwikkeld tegen windpokken (bv Varilrix, Provirax). Een enkele dosis beschermt slechts 72% van de gevaccineerde kinderen en geeft aanleiding tot 'doorbraak windpokken', een meestal mildere vorm van windpokken bij gevaccineerde kinderen. Daarom beveelt men momenteel twee aparte dosissen aan, toegediend aan kinderen vanaf 12 maand. Meer recent is het windpokken vaccin ook beschikbaar als combinatievaccin, samen met vaccins tegen mazelen, bof en rubella (MMR-V, bv Priorix-Tetra, ProQuad). In vergelijking met het windpokken vaccin, wordt na het combinatievaccin meer frequent hoge koorts gezien en treden koortsstuipen op in 1/1100 kinderen ipv 1/2500 na het aparte windpokken vaccin. De vrees bestaat dat deze nevenwerkingen negatief zullen afstralen op de andere routine vaccins die te samen toegediend worden. Bovendien, zoals aangetoond voor andere vaccins, is het profylactische gebruik van paracetamol tegen koorts geen oplossing gezien dit het antwoord door het afweersysteem op het vaccin vermindert.

Een mogelijk effect van windpokken vaccinatie op de incidentie van herpes zoster bij volwassenen, de 'exogene boosting' hypothese. - Het afweersysteem tegen VZV is nog niet goed gekend. Een aantal studies wijzen erop dat volwassenen die vroeger windpokken doormaakten hun immuunsysteem prikkelen telkens ze contact hebben met iemand die windpokken heeft. Dit concept van 'exogene boosting' staat echter nog steeds ter discussie omdat het niet eenduidig bevestigd wordt door surveillance studies. Indien de 'exogene boosting' hypothese juist is, zal een vaccinatieprogramma bij kinderen tegen windpokken aanleiding geven tot een significante stijging van de incidentie van zona bij volwassenen. De lopende windpokken vaccinatieprogramma's in de US, Duitsland en Australië zouden de komende jaren het antwoord moeten leveren.

Onder andere gebaseerd op bovenstaande overwegingen wordt momenteel door de Hoge Gezondheidsraad enkel aanbevolen bepaalde doelgroepen te vaccineren. Daartoe behoren 11 jarigen die nog geen windpokken doormaakten en ad-hoc vaccinatie van volwassenen die geen windpokken doormaakten (met serologische bevestiging), in het bijzonder vrouwen op vruchtbare leeftijd, onderwijzend personeel, en personen die zorg verlenen aan patiënten met een immuun deficiëntie en een negatieve VZV serologie. Deze opties zijn wellicht kosteneffectief zoals vroeger werd aangetoond. In deze studie wordt dit echter niet apart onderzocht.

DOEL

Het doel is het nagaan van de doeltreffendheid and kosteneffectiviteit van verschillende strategieën voor vaccinatie tegen windpokken versus geen vaccinatie in België. De bestudeerde opties zijn vaccinatie tegen windpokken, met en zonder bijkomende booster vaccinatie tegen zona.

METHODE

We gebruiken een dynamisch model dat reeds extensief gebruikt en continu verbeterd is. Dit model voorziet in een leeftijdsgebonden overdracht van VZV. De meeste input variabelen zijn gebaseerd op Belgische gegevens. We hebben bovendien het verlies aan levenskwaliteit gemeten bij kinderen met windpokken (onder de drie jaar), en dit zowel voor kinderen gezien door een arts of niet. Dit is een aanvulling en verbetering ten opzichte van vroegere studies. Ook hebben we het leeftijdsgebonden patroon van sociale contacten gebruikt samen met de Belgische VZV seroprevalentie cijfers die we verzamelden tijdens vroegere studies.

RESULTATEN

Een 2-dosis vaccinatieprogramma bij kinderen zal snel leiden tot een substantiële daling van de incidentie van windpokken bij deze leeftijdsgroep. Daarnaast moeten ook effecten van deze interventie bij de andere leeftijdsgroepen in overweging genomen worden. De kosteneffectiviteit van universele windpokken vaccinatie wordt sterk bepaald door enerzijds het aantal jaren waarover de kosten en effecten van het programma in de analyse worden meegenomen ('de tijdshorizon'), en anderzijds de 'exogene boosting' hypothese.

Indien deze hypothese juist is, verwachten we een sterke toename van het jaarlijks aantal zona gevallen gedurende de 30 tot 50 jaar volgend op de start van het windpokken vaccinatie programma (deelname van 95% op de leeftijd van 1 jaar en een tweede dosis deelname van 90%/80% op de leeftijd van 4/11 jaar). De rol voor een booster vaccinatie op de leeftijd van 60 jaar en ouder is hierbij eerder beperkt, gezien ook een grote toename van zona gevallen verwacht wordt bij personen onder de leeftijd van 60 jaar. De toename van zona gevallen resulteert in een netto verlies aan QALYs gedurende meerdere tientallen jaren. Vaccinatie programma's voor windpokken (apart of als MMR-V combinatie gegeven) zijn onder deze hypothese dus niet doeltreffend noch kosteneffectief gedurende een periode van minstens 40 jaar. Bij lage of matige deelname aan windpokken vaccinatie (bv door terugbetaling van het vaccin zoals de meeste geneesmiddelen) wordt een stijging verwacht van het jaarlijks aantal windpokken bij adolescenten en volwassenen, terwijl de toename van het aantal zona gevallen relatief minder zal zijn over de eerste 35 jaar. Toch wordt ook volgens dit scenario gedurende 70 jaar nog een geaccumuleerd verlies aan QALY's verwacht.

Indien de 'exogene boosting' hypothese niet klopt of bij het hanteren van een tijdshorizon van minstens 40 tot minstens 90 jaar (afhankelijk van de veronderstellingen die men maakt voor onzekere aspecten van de ziektes en het vaccin), is universele 2-dosis windpokken vaccinatie kosteneffectief in België bij de huidige vaccin prijs (€43.46/dosis). De snelle en sterkste daling voor windpokken en de sterkste daling voor zona, kan verwacht worden bij een 2-dosis vaccinatie programma op 1 en 4 jaar en respectievelijke deelnamepercentages van 95% en 90%, ook al is dit strikt gezien niet de meest kosteneffectieve optie. Bij deze strategie vermijdt men ook een stijging van het aantal windpokken bij personen boven de 15 jaar, wat wel een probleem is bij een windpokken vaccinatie deelname van 50% tot 70%.

Momenteel bestaan er enkel indirecte aanwijzingen zowel voor als tegen de 'exogene boosting' hypothese.

DISCUSSIE

Er gebeurde geen probabilistische sensitiviteitsanalyse gezien niet alle parameter-onzekerheid gekwantificeerd kon worden. Bijgevolg kon ook het relatieve belang van de variabelen niet geschat worden. Dit deed men wel in 2010 bij een economische evaluatie van VZV vaccinatie in Engeland & Wales, gebruik makend van hetzelfde dynamische model. Ook al zijn er verschillen tussen België en de UK studies voor de gegevens en de calibratie van het model, toch geeft de UK evaluatie duidelijk aan dat de duur van de 'exogene boost' zeer sterk bepalend is voor de resultaten van universele windpokken vaccinatie bij kinderen.

CONCLUSIE

Indien de 'exogene boosting' hypothese bevestigd wordt, is windpokken vaccinatie bij kinderen in België niet kosteneffectief gedurende vele tientallen jaren. Dit komt door een verwachte toename in het jaarlijkse aantal gevallen van zona (herpes zoster) na de start van zo een vaccinatie programma. Indien integendeel deze 'exogene boosting' hypothese niet klopt, is grootschalige windpokken vaccinatie met een 2-dosis regime wellicht kosteneffectief in België aan de huidige vaccinprijs.

VACCINATIE TEGEN ZONA (HERPES ZOSTER) BIJ OUDEREN

INTRODUCTIE

Een hoger gedoseerd afgezwakt levend VZV vaccin is ontwikkeld tegen zona (Zostavax). Een enkele dosis toegediend aan 60 plussers vermindert de incidentie van zona gedurende de drie jaar na vaccinatie, in vergelijking met placebo. De werkzaamheid daalt echter continu met de leeftijd, van 64% bij de 60-69 jarigen tot 38% boven de leeftijd van 70 jaar. Bij 80 plussers werd geen statistisch significante werkzaamheid aangetoond. Er zijn geen robuuste gegevens beschikbaar over de werkzaamheid na meer dan 5 jaar, en of het vaccin werkzaam is bij personen met een verminderde werking van het immuunsysteem.

DOEL

Het doel van deze evaluatie is het onderzoeken van de kosteneffectiviteit van universele vaccinatie tegen herpes zoster versus geen vaccinatie in België, en dit voor verschillende leeftijdscohortes (60 tot 85 jaar).

METHODE

We ontwikkelden een deterministisch gecompartimenteerd statisch model waarbij de personen volgens hun leeftijd herpes zoster kunnen doormaken. Bijna alle input variabelen van dit model zijn geschat gebruikmakend van Belgische gegevens. Gezien leeftijd een belangrijke covariaat is voor de incidentie van zona, werden bijna alle input variabelen geschat volgens leeftijd, behalve het deel van de gehospitaliseerde zona patiënten dat geen huisarts opzocht. Dit is ook de eerste studie die zona-gerelateerd kosten en verlies aan QALYs inschat in functie van een score voor duur en ernst van de ziekte (severity of illness score, SOIS). Teneinde leeftijdsgebonden en SOIS specifieke schattingen te verkrijgen, hebben we de gegevens gefit met flexibele statistische modellen. Een nadeel hiervan is dat het zo moeilijk of onmogelijk wordt om parameter onzekerheid te kwantificeren. Daarom werd ook geen probabilistische sensitiviteitsanalyse uitgevoerd. De onzekerheid is echter afhankelijk van onzekerheid van het model, de brongegevens en gebruikte methode. Deze laatste types onzekerheid werden meegenomen bij het uitvoeren van een worst case (anti-vaccine) en best case (pro-vaccine) scenario. De impact hiervan op de doeltreffendheid en kosteneffectiviteit van zona vaccinatie op verschillende leeftijden werd onderzocht met univariate en multivariate scenario analyses.

RESULTATEN

Voor verschillende belangrijke variabelen bestaat nog grote onzekerheid rond de keuze van de gegevensbron en/of het te gebruiken model om die variabelen te schatten. Deze onzekerheid neemt toe met de leeftijd van de te vaccineren cohorte. Zoals aangetoond in de onderstaande tabel, heeft dit een grote impact op de kosteneffectiviteit in België.

Tabel A: Kost per gewonnen QALY voor zona vaccinatie van verschillende leeftijdscohortes (tot einde levensloop). Kosten zijn verdisconteerd aan 3%, effecten aan 1.5%. 'Best' respectievelijk 'worst case' scenario, is een scenario waarbij voor vijf inputvariabelen, die waarde gekozen wordt die meest gunstig, respectievelijk minst gunstig is voor zona vaccinatie.

		Leeftijdscohorte			
		60j	70j	80j	85j
Kost per gewonnen QALY (in EURO)	'best'	1251	2294	3988	5498
	'worst'	48978	73513	132220	303705

DISCUSSIE

Veel onzekerheden die we trachten te kwantificeren en te bespreken in deze studie bleven onbehandeld in vorige studies, die dikwijls gesponsord waren door de industrie. We beschouwen het erkennen van de onzekerheden en het opsplitsen van de outcome in functie van de leeftijd (in jaren) als een belangrijke bijdrage van deze studie aan de internationale literatuur. Een grote prospectieve studie met meting van de leeftijds-specifieke ernst van ziekte (SOIS) en verlies aan QALYs bij zona in de algemene bevolking zou zeer nuttig zijn om onze analyses rond dit onderwerp te verfijnen.

Verder is er momenteel nog een gebrek aan publiek beschikbare informatie rond de werkzaamheid van het vaccin over de tijd in combinatie met de leeftijd, werkzaamheid volgens bewaring van het vaccin (ingevroren of niet), en welke groepen mogelijks baat kunnen hebben van vaccinatie (bv. personen die immunocompetent zijn of niet). Ook is het cruciaal te beschikken over input parameters per leeftijd (in jaren) om de leeftijd te kunnen berekenen waarop vaccinatie het meest kosteneffectief is.

CONCLUSIE

Bij de huidige vaccinprijs is het vaccineren tegen zona van 60 plussers in België niet kosteneffectief onder de ‘worst case’ assumpties. Het vaccineren van 65 plussers is bij de meeste scenario’s minder kosteneffectief dan vaccinatie op de leeftijd van 60-64 jaar.

AANBEVELINGEN[a]

- **Een veralgemeend vaccinatie programma tegen windpokken (of andere vormen van grootschalige vaccinatie zoals bij terugbetaling door een aantal mutualiteiten) kan niet aanbevolen worden. Er bestaat namelijk een redelijk risico dat deze interventie meer nadelen dan voordelen heeft voor de volksgezondheid.**
  Deze aanbeveling dient te worden herzien indien blijkt dat er geen stijging optreedt van het aantal zona gevallen in de weinige landen die gestart zijn met grootschalige vaccinatie tegen windpokken. Daarbij dient ook rekening te worden gehouden met het belang van de deelname aan de vaccinatie.
- **Vaccinatie van volwassenen en ouderen tegen zona (herpes zoster) wordt niet aanbevolen gebaseerd op de huidige analyses van de kosteneffectiviteit aan de huidige vaccinprijs.**

  Deze aanbeveling dient te worden herzien bij het beschikbaar komen van gegevens die een meer accurate en robuuste inschatting van de kosteneffectiviteit toelaten.
- **Industrie en agentschappen voor geneesmiddelen dienen bewust te zijn van het belang van het publiek toegankelijk maken van alle studie-resultaten die cruciaal zijn om de accuraatheid te verhogen van de analyses naar kosteneffectiviteit.**

<u>Onderzoeksagenda:</u>

- **Een grote prospectieve studie naar de leeftijdsgebonden ernst van zona en het verlies aan levenskwaliteit in de algemene bevolking is noodzakelijk.**

a Alleen het KCE is verantwoordelijk voor de aanbevelingen aan de overheid.

Scientific summary

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1 GENERAL BACKGROUND

Varicella zoster virus (VZV) is a DNA virus and a member of the herpes virus family. It is also known as human herpes virus type 3. Primary infection with VZV results in varicella, which is commonly known as chickenpox (CP), and mainly occurs in childhood. Following primary VZV infection, the virus migrates to the dorsal root or cranial sensory ganglia and remains there in a latent state. However, VZV may reactivate at a later stage in life, resulting in herpes zoster (HZ), which is commonly known as shingles.

1.1 CLINICAL MANIFESTATIONS

Chickenpox (CP) is usually a mild disease of short duration in healthy children. The incubation period ranges from 7-21 days followed by a prodrome period lasting 1-2 days with fever and malaise, and then the characteristic appearance of macules, papules, vesicles and crusts together[1]. Whereas on average 250-500 lesions occur during a typical CP episode, the final number of lesions may be as many as 1500[1]. About 5% of cases are either atypical or asymptomatic[1]. However, complications from CP, including bacterial skin infection, pneumonia and encephalitis occur in approximately 1% of cases[2]. The frequency of complications is greater in adolescents, adults and the immunocompromised. Chickenpox is very exceptionally lethal (see further below), and potentially so at any age, including in otherwise healthy people. Because it is highly infectious and very prevalent at a young age, it is expected to commonly give rise to physician consultations, and hospitalisations. Chickenpox in pregnant women (especially between 13-20 weeks gestation) is associated with a 2% risk of congenital varicella syndrome (CVS)[3]. CVS can cause central nervous system damage, limb hypoplasia, skin scarring, eye defects and deaths[4]. Foetuses with intrauterine exposure (especially between 25-36 weeks gestation) also have a 0.8-1.7% risk of developing HZ in infancy[3]. Perinatal maternal varicella can result in severe neonatal varicella infection. Maternal infection starting 5 days before delivery and up to 2 days after delivery is estimated to result in severe varicella in 17-30% of newborns, with a mortality rate up to 30%[5].

Reactivation of latent infection, causing HZ results in a unilateral rash in a dermatomal distribution that is often painful[1]. Pain associated with HZ may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the reactivation. Pain occurring in the postherpetic phase of VZV reactivation is commonly referred to as postherpetic neuralgia (PHN). Other complications associated with HZ, such as ophthalmic disease, can occur depending on the site of reactivation. In addition, dermatomal pain can occur without the appearance of a rash (zoster sin herpete). Hope-Simpson estimated the lifetime risk of reactivation of HZ at approximately 15%[6]. HZ occurs more commonly with increasing age (>50 years), immunosuppression and a history of CP in the first year of life. Post-herpetic neuralgia (PHN) occurs rarely in young persons, but may be associated with 20-50% of patients who develop HZ over the age of 50 years[1, 7].

1.2 TRANSMISSION

VZV is transmitted by respiratory air droplets and vesicle fluid during ordinary social contacts. A person who is infected with chickenpox can transmit the virus for about 7 days, until the lesions have formed crusts. It is assumed that natural infection with VZV confers lifelong immunity. Most transmission occurs between children (i.e. mainly in day care centres, kindergarten, schools and households).

In temperate regions, generally more than 90% of the population has acquired immunity to VZV by age 15 years. This is documented by serological studies,[8-14] including in Belgium (see also below)[15-18].

Zoster lesions contain high concentrations of VZV that can be spread and infect susceptible contacted persons after the rash erupts and until the lesions crust, presumably by the airborne route[19-21]. In household situations HZ can be estimated to be about 4.6 times less likely to infect susceptible household contacts than chickenpox[20,22].

There is evidence to suggest that exposure to CP might reduce the risk for HZ. This mechanism of exogenous boosting of VZV-specific immunity was suggested based on three analyses conducted in the United Kingdom[23-25], Garnett and Grenfell[24] showed an inverse relation between annual CP incidence in children aged <5 years and HZ incidence in adults aged 15–44 years. In a case-control study Thomas et al[25] found the risk of HZ to decrease as a function of the number of CP contacts over a 10-year period (up to 74% reduction among persons with three to four varicella exposures compared with those with no exposure). Brisson et al[23] used data from a GP network to conclude that adults living with children <16 years experienced more CP and less HZ than adults who did not. In other studies, household exposure to CP reduced the development of HZ amongst children with leukemia[26], and the fact that Zostavax® vaccine is efficacious in reducing the risk of HZ[27] supports the notion that exposure to VZV may boost specific immunity against developing HZ.

This concept is still somewhat disputed, since there is also contradicting evidence: women seem at greater risk for HZ[21], while they are likely to be, on average, more frequently exposed to CP than men, and one Japanese study[28] found no reduced HZ risk amongst children who had been repeatedly exposed to CP.

2 DATA SOURCES AND INTERMEDIARY DATA ANALYSES

2.1 DATA SOURCES

2.1.1 MCD-HBD

The registration of MCD (Minimal Clinical Data, or 'Minimale Klinische Gegevens/ Résumé Clinique Minimum') is mandatory for every hospital in Belgium since 1991. This means that for each hospitalized patient, information such as birth date, address, gender, and other information such as length of stay (LOS) in the hospital, diagnosis, techniques used and treatments have to be recorded and sent to the FOD (Federal Government administration). Data are stripped from patient-identifying information. These data are coupled with the HBD (Hospital Billing Data), which records the (public) health insurance costs of each hospital stay. This means that the relationship between treated pathology and the costs to the health care system can be studied. The advantage of the coupled MCD-HBD data is that it is obligatory for all hospitals. However, one should keep in mind that we do not know how accurate each hospital reports the obligatory MCD data, nor how reliably the data are gathered. Hence, interpretation of the data should be done with care.

From this database, we obtained data on varicella-zoster associated hospitalisations, (with ICD9 CM codes 052.*and 053.0* in any diagnostic field for the period 2000-2007).

2.1.2 Carenet

The concept of Carenet is designed for the exchange of information about hospital admissions, length of stay and costs of hospitalisations between hospitals and health insurance companies through an electronic system (internet platform). All Belgian health insurance companies participate in the project in a national intermutualistic context. Information (names, location) of hospitals currently joined in Carenet is available at http://www.carenet.be/nl/ (accessed 17/02/2010).

We obtained access to Carenet data on hospitalized patients who were members of the National Christian Sickness Fund (NCSF or 'Christelijke Mutualiteiten/Mutualité Chrétienne', see further). The general database from the NCSF contains all resource use information of members of the largest sickness fund in Belgium. The membership population of NCSF corresponds to 43.7% of the total Belgian population. There is a slight bias in favour of the older age groups, but this should not grossly distort the estimates based on NCSF members. In terms of socio-economic characteristics, the unemployed are slightly underrepresented (40.6% of the unemployed are members), but, again, the overall difference is relatively limited (i.e. 43.7% versus 40.6%).

All Carenet registries starting from 01/05/2006 for which the diagnostic field contained 'wijnpokken', 'windpokken', 'waterpokken', 'varicell', 'zona', 'zoster', 'gordelroos', ICD code '053' or code '052' were retrieved, and analysed after personal identifiers were removed. A medical clinician searched the diagnostic fields of the retrieved records manually and removed all hospitalisations that were unlikely to be due to varicella-zoster virus (or for which this was unclear). Note that this Carenet database is not used to estimate incidence (see further).

Two datasets of NCSF members were thus compiled:

1. Patients who were hospitalised for CP (2006-2009).
2. Patients who were hospitalised for HZ (2006-2009).

Both datasets contain for each patient their diagnoses during hospitalisation, length of stay in the hospital, age, gender, costs to the National Health System (NHS, i.e. direct health care costs for RIZIV/INAMI) and co-payments by patients and their private insurance (mainly 'remgeld' and 'supplementen'). Moreover, based on the complete description of the diagnoses, a medical clinician categorised the CP patients according to complication (see further).

These datasets are used primarily to identify NCSF members who were hospitalised for CP or HZ, so that they could be surveyed regarding their disease experience and costs incurred (see next section). Furthermore these datasets are used to estimate CP and HZ hospitalisation rates by age, gender and to assess whether there is seasonality in these data. These last estimates are not used as inputs of the model, but to cross-validate similar national data obtained from the MCD database (described above), which covers the complete Belgian population.

These data extractions and associated analyses were performed at the Medical Management Department of the National Alliance of Christian Mutualities under supervision of a medical advisor, and data were processed on an anonymous basis.

2.1.3 Surveys amongst NCSF members

Four retrospective surveys were set up to obtain detailed information on the following aspects of CP and HZ patients and their caregiver(s): medical costs (consultations, medication, etc) and non-medical indirect and personal costs (e.g., transportation, absenteeism from work...), as well as general background and LOS in hospital for hospitalized patients. We aimed to obtain these data for patients who recently experienced CP or HZ, covering both those who were hospitalised and those who were not. For all 4 surveys, 11 NCSF nurses (7 Dutch- and 4 French-speaking) sent personalised letters to eligible NCSF members in all the provinces of Belgium, together with a questionnaire they were asked to prepare answers for (example questionnaires (in Dutch and French) can be found in Appendix 1). A few days later, the nurse contacted the eligible person by phone, went through the questionnaire, and wrote down the answers.

Data related to hospitalized CP and HZ patients

The survey sample was extracted from the Carenet database described above. For all patients who were hospitalised more than once for CP or HZ, the survey focused only on the most recent hospitalisation (the sample was derived based on unique patients, rather than unique hospital admissions). For CP, 300 patients were drawn from the most recent complete calendar years. Complete years were taken, as explorative analyses showed CP incidence to be seasonal in Belgium (see below). For HZ, the 900 most recent hospitalised patients were selected. The predefined sample size was 60 completed questionnaires for CP and 180 completed questionnaires for HZ. The representativeness of the samples relative to the complete Carenet datasets was checked in terms of gender, age, length of stay, and for CP only, season and complication group.

After removing from the HZ and CP samples people who had died, the remaining persons were contacted to complete a questionnaire (described before). Besides some background information, it gives an overview of all cost items outside the hospital stay that make up the total health care payer's cost, as well as co-payment of the patient and his/her private insurance (mainly remgeld+supplements) for a CP and HZ episode.

In-hospital health care costs (attributable to CP and HZ) of the sampled patients were extracted from Carenet.

Data related to CP and HZ patients treated on an outpatient basis

The NCSF launched an appeal on their website (Dutch and French, mid October 2009), in their monthly periodical 'Visie' (23rd October 2009) and 'En Marche' (15thOctober 2009) to people who had experienced HZ over the last year, but were not hospitalised for this HZ episode. The NCSF also launched an appeal on their website (Dutch and French, end January 2010), in their monthly periodical 'Visie' (29 January 2010) and 'En marche' (4 February 2010) to people who experienced CP over the last 6 months, without being hospitalised for this CP episode. Such interested NCSF members were thus requested to participate on a voluntary basis in a written questionnaire. The questionnaire presented to these non-hospitalised NCSF members was the same as that for the hospitalised members, except for the questions about hospitalisation.

2.1.4 Child & Family survey

Child & Family ('Kind & Gezin') is a Flemish governmental agency with responsibility of young children and families in Flanders, in particular in the fields of preventive care, child care services, family support, diversity and children's rights (http://www.kindengezin.be/English_pages/default.jsp, accessed 17/02/2010). About 70% of children aged 0 to 3 years undergo regular check-ups at the Child & Family consultation offices, located throughout Flanders.

Since the international literature shows a general lack of surveys into the quality of life of the most common manifestation of CP, uncomplicated ambulatory CP, we set up a survey to estimate the loss in Quality of Life (QoL). The goal was to obtain 20 completed questionnaires in each of the 5 Flemish provinces: 10 from an urban and 10 from a rural consultation office (except for 'Vlaams-Brabant': 3 rural offices and 1 urban office aimed to gather 5 completed questionnaires each). The survey is in Dutch and loss in QoL is measured using the EQ-5D. The questionnaire was completed by parents/carers of children who experienced CP over the 6 preceding months.

Although the survey will primarily include children <3 years of age, who are Dutch-speaking and living in Flanders (patterns in visiting GP as opposed to paediatricians may be different in Brussels and Wallonia), it is at this moment the only way for us to actually measure the loss in Quality of Life (QoL) in a reasonably representative sample of children with various manifestations of CP.

This survey started in mid-February 2010 and data received up to the 7th of July 2010 were used in the analysis.

2.1.5 Social contact patterns

The Centre for Health Economics Research and Modelling Infectious Diseases (CHERMID) of the Vaccine & Infectious Disease Institute at the University of Antwerp in collaboration with the Centre for Statistics (Censtat) of Hasselt University derived social contact patterns relevant to the spread of VZV based on a survey amongst the Belgian population. Over the period March – May 2006, 750 persons living in Belgium were recruited by random digit dialing. Only one person per household could participate. Participants were recruited from the Flemish (n = 441), Walloon (n = 239) and Brussels geographic regions (n =70)[29, 30]. Two types of physical contacts were defined: (1) two-way conversations during which at least three words were spoken without raising one's voice; (2) contacts which involved skin to skin touching. Each participant was asked to fill in a paper diary recording their contacts during one randomly assigned weekday and one randomly assigned day on the weekend. Further details of this study can be found elsewhere[29, 30].

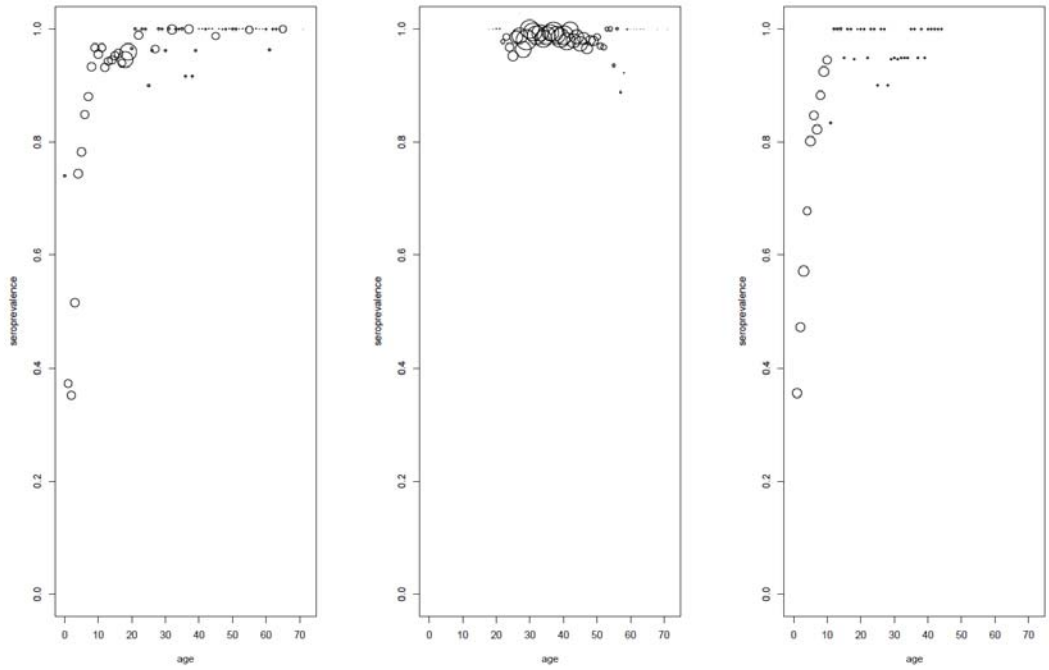
These contact patterns have been shown to perform better in dynamic transmission models for VZV[31] than previously assumed contact patterns[32]. How this dataset is used in this report is described below under methods.

2.1.6 Serological surveys

The Centre for the Evaluation Vaccination of the Vaccine & Infectious Disease Institute at the University of Antwerp conducted two general seroprevalence surveys in the Belgian population. The first tested blood samples between October 1999 and April 2000 obtained from 1673 persons aged 1-44 years, using a variety of sources in the province of Antwerp: outpatients at a large children's hospital (1–12 years); volunteers in vaccine trials at CEV (12–16 years); a large medical laboratory (>16 years)[17]. The second tested 3256 blood samples (excluding equivocal results) collected between November 2001 and March 2003, in ages 0-80 years[15]. Together with the test result, the gender and age of the individuals were recorded.

Additionally, the occupational health service ("IDEWE") collected blood samples amongst 4923 employees (4826 excluding equivocal results) of 22 hospitals in the Flemish and Brussels regions from February 1996 to June 1997[18]. The results obtained from the three samples compare well (Figure 1). For the purpose of the current analysis, we will use the most recent and most representative dataset, namely the Belgian sample from 2001-2003[15].

Figure 1: Proportion varicella-zoster virus immune by age (in years) in three Belgian seroprevalence studies (left: general population 2001-2003; middle: Flemish hospital employees 1996-1997; right: Antwerp population 1999-2000; size of circles proportionate to sample size).



2.1.7 Flemish Agency for Care and Health

The Flemish Agency for Care and Health (FACH, 'Vlaams Agentschap Zorg & Gezondheid/L'Agence flamande Soins et Santé') registers the causes of death (ICD10 code) by year, gender and age for habitants of 'het Vlaamse Gewest' who died in 'het Vlaamse of Brusselse Gewest'. So people who died abroad or in 'het Waalse Gewest' are not included. Causes of death are derived from the death certificates, which are filled in by the medical doctor and completed by 'de dienst burgerlijke stand' of the municipality ('gemeente') of the deceased person (http://www.zorg-en-gezondheid.be/sterftecijfers.aspx, accessed 17/10/2010).

FACH provided us with all death certificates from 1998-2007 that contained ICD10 codes B01 and B02 in any cause of death field. These death certificates were screened by expert clinicians, who indicates which of these deaths were likely avoidable through the avoidance of CP or HZ episodes.

We have launched similar requests to the Brussels and Walloon death registries, but these data did not arrive in time to be included in this report.

2.1.8 Scientific Institute of Public Health (SIPH)

The SIPH (Scientific Institute of Public Health or 'Wetenschappelijk Instituut Volksgezondheid/Institut Scientifique de Santé Publique') has a sentinel system of general practitioners. The Sentinel General Practitioners (SGP's) are a selection of 150 medical practitioners and reach about 1.5% of the Belgian population (1.6% of the Flemish and Walloon population and 0.9% of the population in Brussels). The participating sentinel general practitioners are representative of the total group of Belgian GP's in terms of sex and age (with exception of an overrepresentation in the age group 40-49 years)[33].

The SGP's register the first consultation of a new episode of CP and HZ, which – in combination with catchment population estimates - enable estimates of the annual rate of patients with CP and HZ who visit a GP at least once. Note that such estimates represent 'minimum' estimates for the CP and HZ related ambulatory visits, because patients who consult specialists (e.g. paediatricians or dermatologists) directly, without consulting a GP first, are not included.

To obtain information on the proportion of all HZ patients who visit a GP, but who are not hospitalized, the following 2 questions are added to the standard surveillance questionnaire for each diagnosed HZ patient by the SGP's:

1. Was/is the patient hospitalised because of this HZ episode? (yes/no/don't know)
2. How long was your patient sick because of this HZ episode? (please answer as accurately as possible (e.g. number of days))

Additionally, a follow-up form was completed 3 months later, which contains the following questions:

- Was your patient hospitalised because of the HZ for which s/he visited you 3 months ago? (yes/no/don't know)
- How long was your patient sick because of the HZ for which s/he visited you 3 months ago? (please answer as accurately as possible (e.g. number of days))

2.1.9 Scott et al (2006) data

Scott et al[34] conducted a prospective observational study in East London. They followed for 8 months all HZ cases referred by a group of general practitioners in East London within 7 days of rash onset or with active vesicles, and recorded their severity of pain, duration of pain and loss in quality of life (QoL), among other characteristics. Only HZ cases confirmed to be VZV by PCR were included (N=65). Mean age of the persons followed during the study is 50.7 years (range 10-85 years), 25 of them being older than 65. This is the only study we are aware of, which covers all HZ patients who seek medical care (i.e. not restricted to the most severe ones or to a certain age group). As it is a well-conducted study, we use the data from this study to quantify the age-specific average loss in QoL for an average HZ patient seeking medical care. Also, this data set is used to check the representativeness of the people included in our Belgian survey samples in terms of average severity and duration of HZ pain, and if necessary, to adjust our samples for possible bias. The authors of this paper were contacted and we were fortunate to obtain their permission to work with their raw dataset (Personal communication, Scott & Edmunds, 2009).

2.1.10 Scientific literature

We consulted the scientific literature to obtain a number of important parameters we could not generate ourselves within the time frame and budget restrictions of our study. These include the Zostavax® vaccine efficacy and effectiveness, and CP vaccine efficacy and effectiveness. Additionally literature sources are used to validate some of the other epidemiological, immunological and cost parameters.

2.2 HOSPITALISATIONS, PHYSICIAN CONSULTATIONS AND DEATHS DUE TO CHICKENPOX AND HERPES ZOSTER

In this section, we outline some important population-level consequences of VZV infections. These consequences in terms of hospitalisations, physician consultations and deaths were specified according to age. Where possible, HZ-related consequences are also specified according to immune status (immunocompetent/ immuncompromised). Whereas immune status is likely to have little influence on the occurrence of CP consultations and deaths, HZ is much more common in people with diminished cell mediated immunity. This includes elderly people, patients with lymphoma, those receiving chemotherapy or steroids, and HIV positives[35]. Some disagreement exists on the possible predictors for PHN, partially due to the use of different definitions for PHN. However, older age and greater acute pain are consistent predictors throughout all studies[7, 36-38]. Therefore, the occurrence of PHN is estimated by age.

The yearly age-specific numbers of cases hospitalised, cases consulting a physician anddeaths were divided by corresponding age-specific Belgian population data to obtain annual hospitalisation rates, annual rates of physician consultations and death rates due to CP and HZ. Rather than using Belgian demographic data from a single or several years, a Gompertz curve was fitted on these data (obtained from Statbel: http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/structuur/leeftijdgeslacht/belgie/index.jsp, accessed 17/02/2010).

2.2.1 Hospitalisations due to CP and HZ

2.2.1.1 Hospitalisations extracted from the MCD database

Hospitalisations due to CP (MCD)

There is a seasonal trend in the hospitalisations of CP with an annual peak in April through June (Figure 2).

Figure 2: Number of chickenpox hospitalisations per month as primary diagnosis only and as primary or secondary diagnosis (MCD database, 2000-2007).

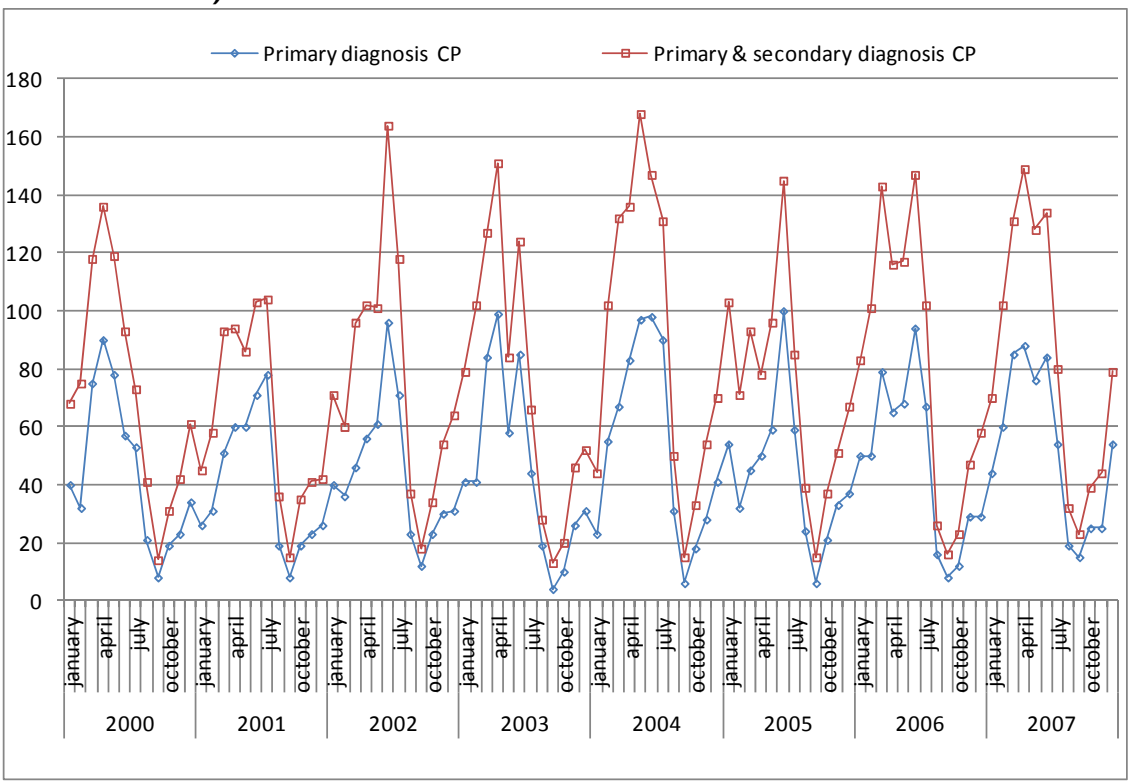
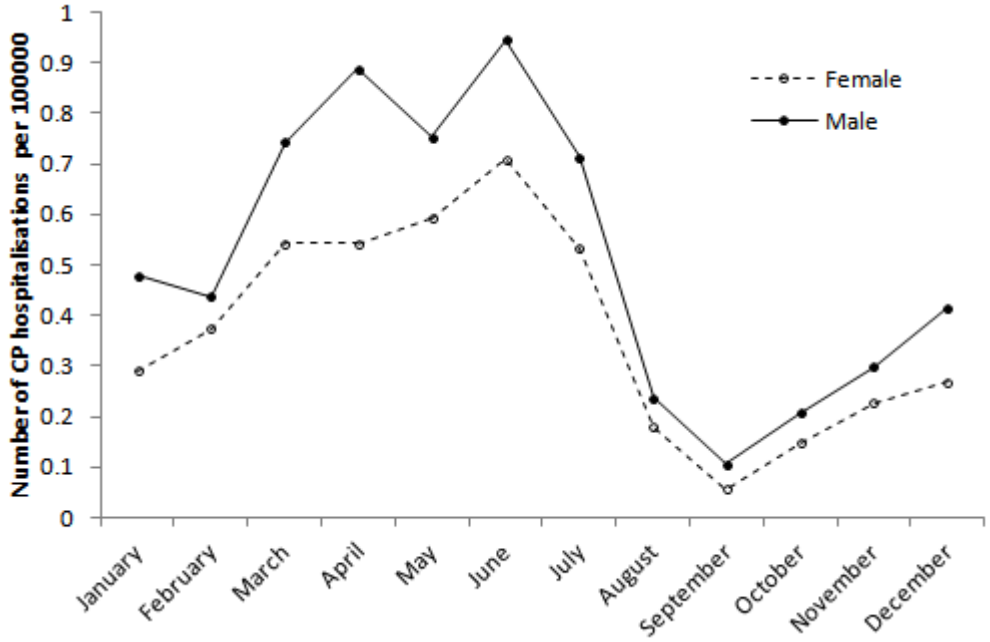


Figure 3 shows the seasonal chickenpox pattern averaged out over the years, and indicates that the hospitalisation rate is markedly lower for girls than for boys.

Figure 3: Average number of hospital admissions per month per 100,000 population for primary cause CP, by gender (MCD database, 2000-2007)



The age at hospitalisation in the MCD database is not very precise, as it is calculated as the difference between the year of hospitalisation and the year of birth. Consequently, the number of cases in the <1 year old population will be underestimated. For instance, a child born in September 2007, suffering from CP in January 2008, will be categorised as being 1-year old when having CP, whereas his/her through age when having CP is only five months. This systematically underestimation of hospitalisations in the less than 1 year old age groups, does not happen for other age groups, as these groups will contain patients with actual ages being younger and older. Because the CP hospitalisation rate for less than 1 year old patients is not reliable, the age distribution of CP hospitalisations is not shown here.

Hospitalisations due to HZ (MCD)

As the number of HZ hospitalisations does not vary substantially between years, data are grouped over the years to get HZ hospitalisation rate by age, gender, primary/any diagnosis and immune status.

The HZ hospitalisation rate in Belgium is shown in Figure 4 by year, age and for hospitalisations with HZ as primary diagnosis, and as any diagnosis (primary+secondary) separately. Figure 5 shows the *number* of hospitalisations with HZ as primary and any diagnosis by age and gender for Belgium, and Figure 6 shows the hospitalisation *rate* by diagnosis, age and gender.

Figure 4: Number of HZ hospitalisations per 100,000 population, stratified by year, age and HZ as primary or as any (primary & secondary) diagnosis (MCD database, 2000-2007).

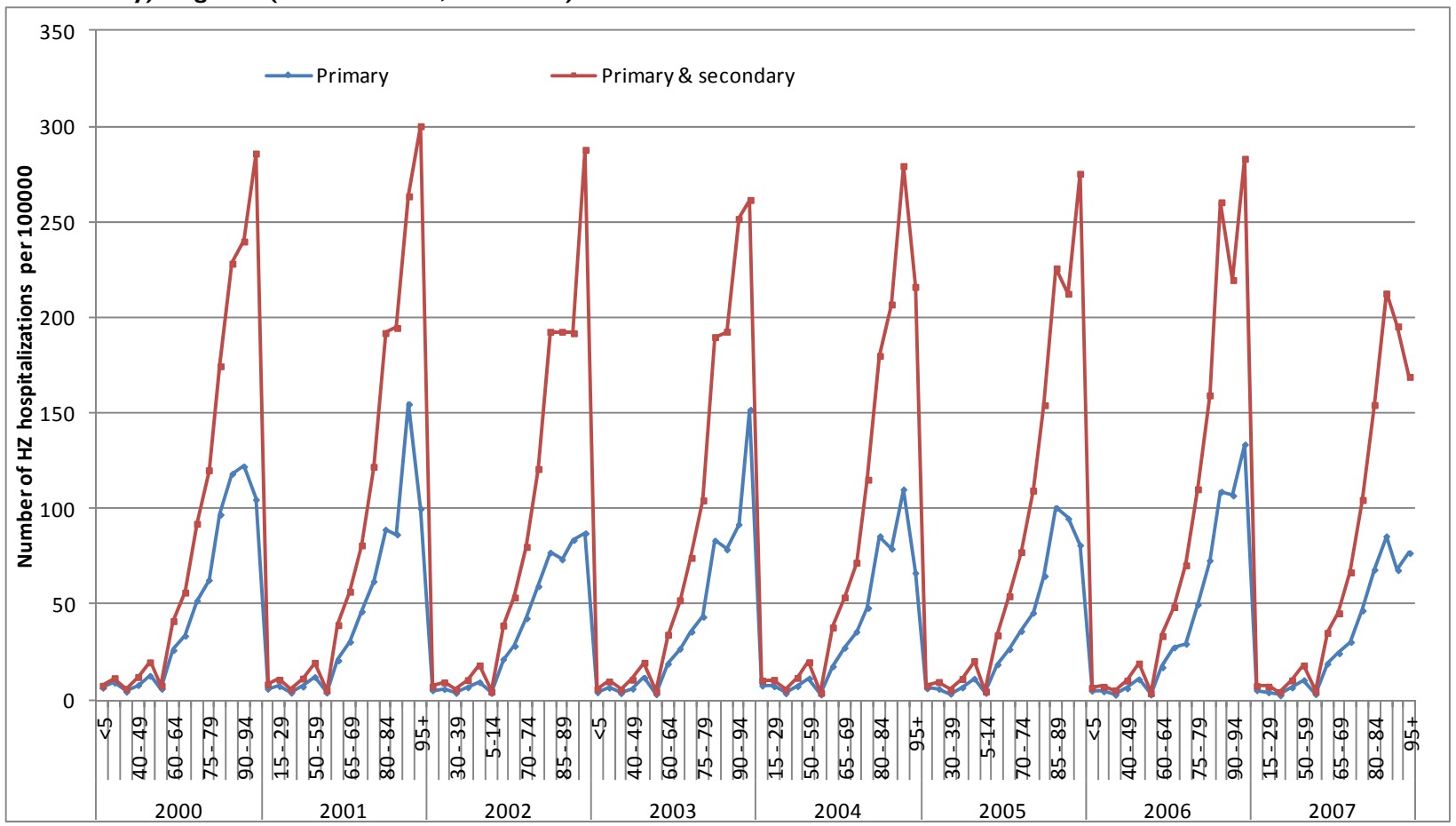


Figure 5: Number of HZ hospitalisations by age (continuous) and gender (MCD database, average 2000-2007).

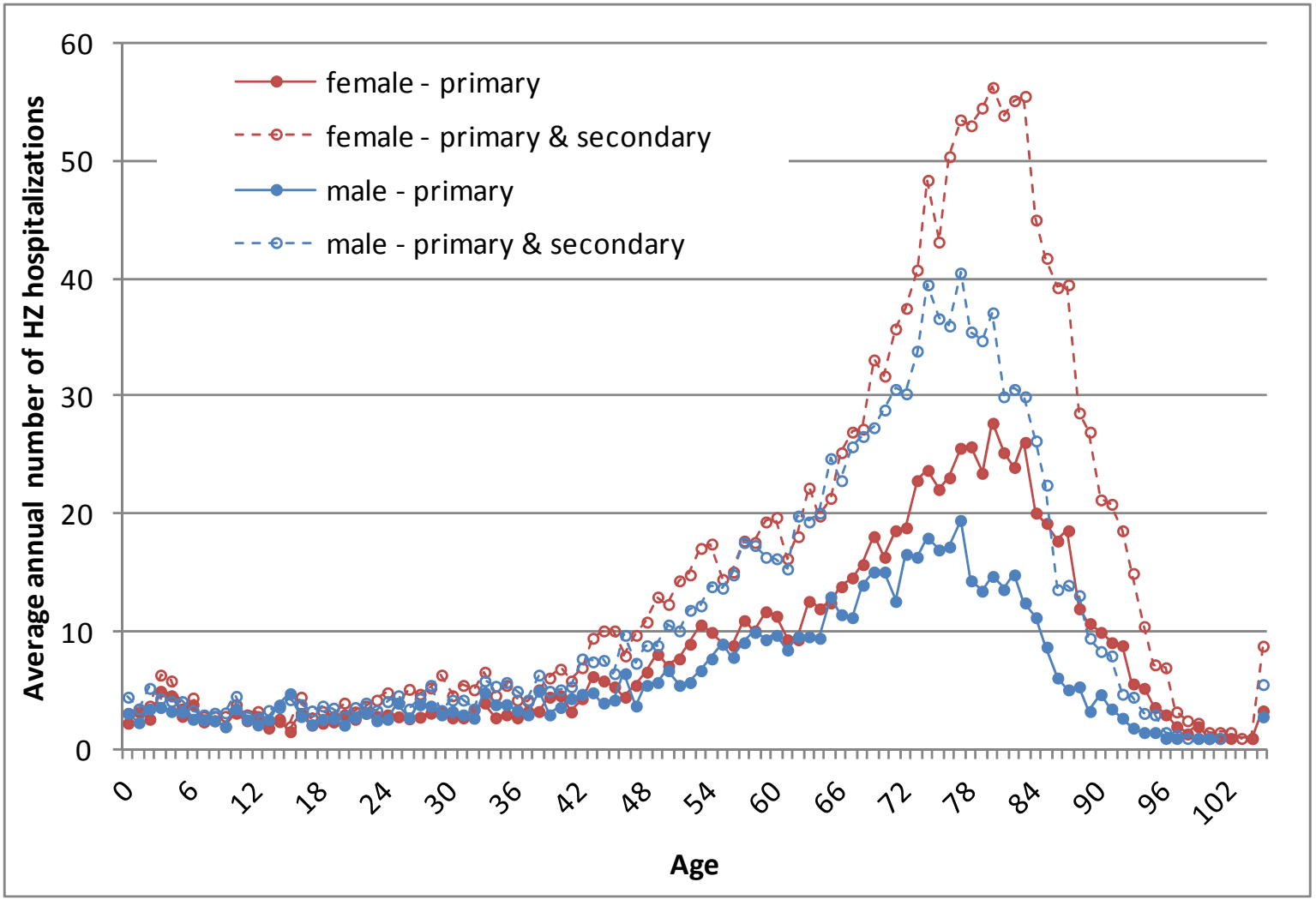
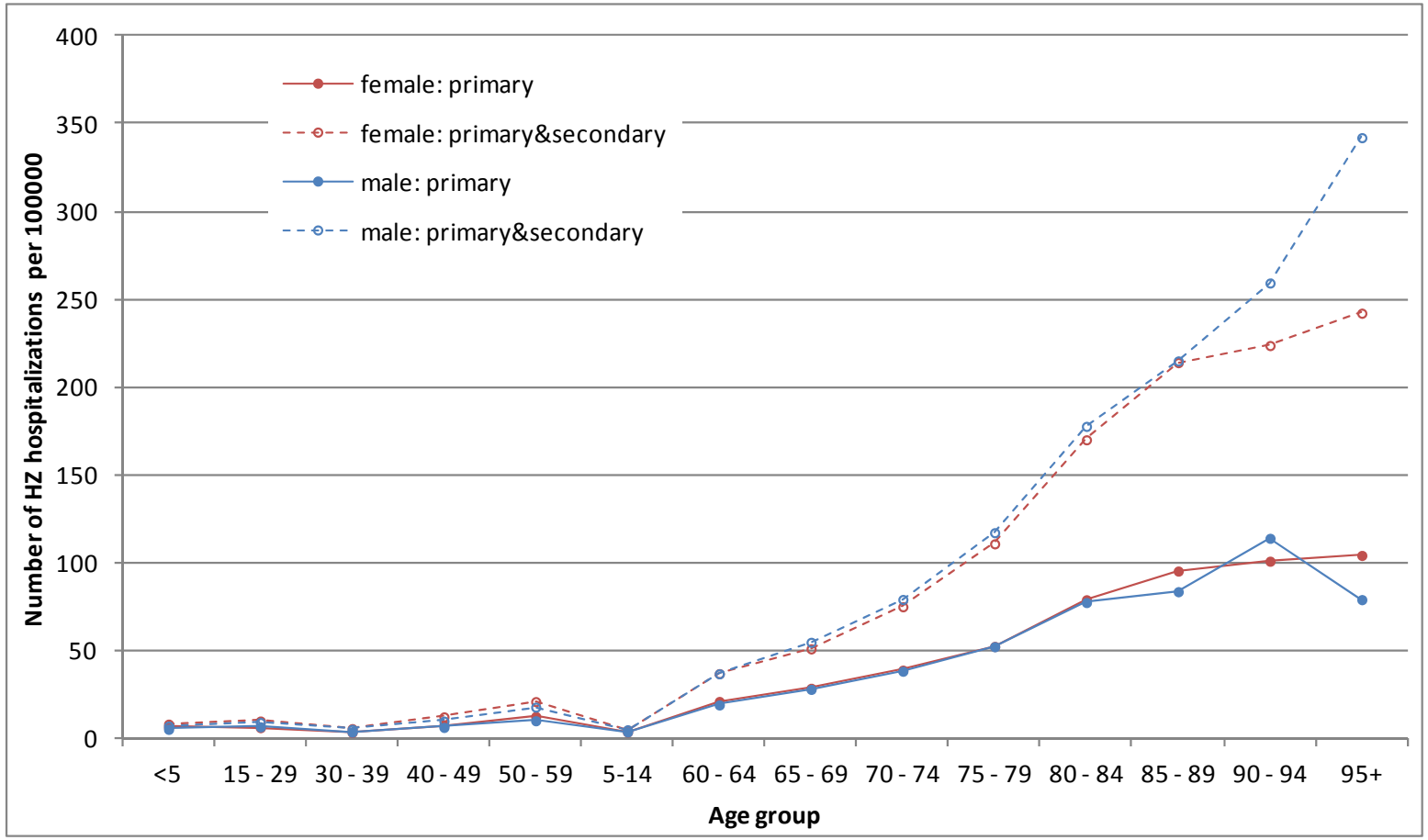


Figure 6: Number of HZ hospitalisations per 100,000 population with HZ as primary or any (primary & secondary) diagnosis, stratified by age and gender (MCD database, 2000-2007).



2.2.1.2 Hospitalisations extracted from the Carenet database

The CP and HZ hospitalisation rates we use in model projections (see below) were obtained from the MCD database. However, for cross validation, we will also estimate hospitalisation rates using Carenet.

Extraction of hospitalisations from Carenet

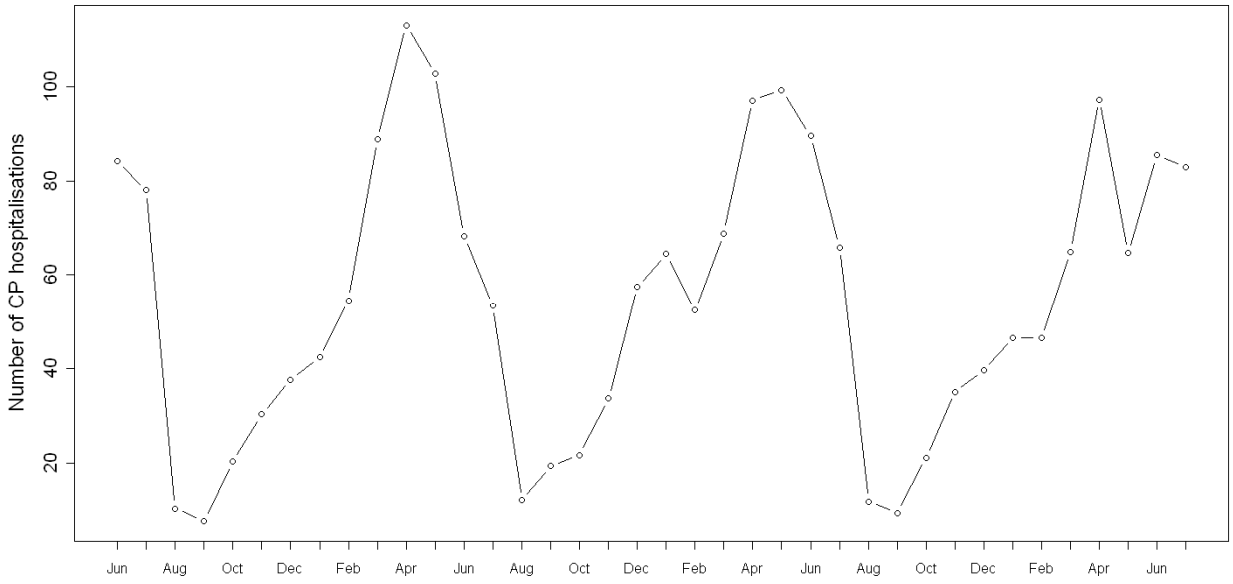
In order to arrive at estimates for hospitalisation rates in Belgium, we first divided the number of hospitalisations by 0.437, since NCSF covers 43.7% of the Belgian population. This gives the number of hospitalisations for the complete Carenet population. Next, the number of hospitalisations is adjusted according to the number of hospital beds covered by Carenet (Carenet does not cover 100% of the beds in Belgium). The coverage of Carenet ranged from 87.97% in July 2006 to 99.23% in July 2009. Since the percentage covered is not available at each month, a linear and logarithmic curve was fitted to the coverage data and the best fit (the logarithmic curve) was used to estimate the missing data points.

The number of hospitalisations from the Carenet database was adjusted by dividing these numbers by the coverage of the Carenet database. This gives an estimated number of hospitalised CP and HZ cases for the Belgian population.

Hospitalisations due to CP (Carenet)

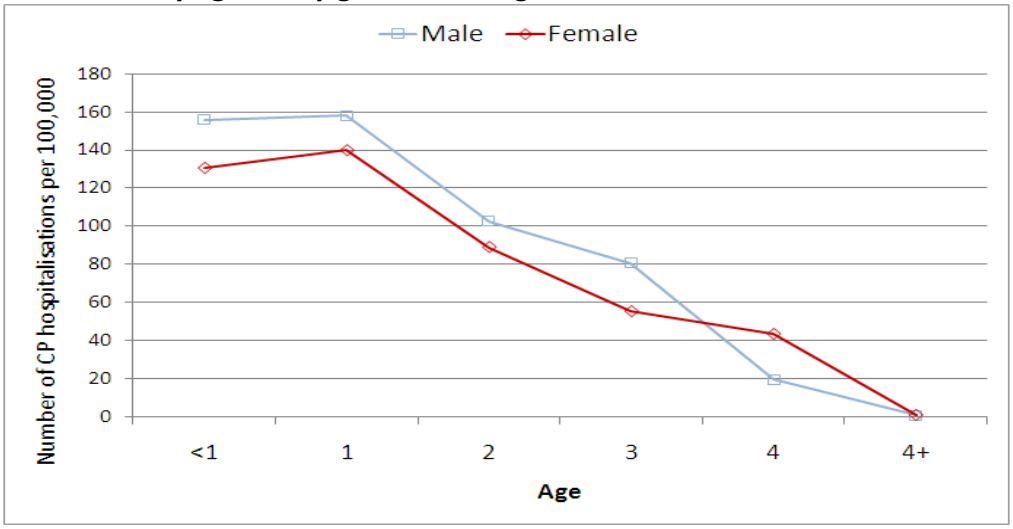
Thirteen patients had 2 hospitalisations for CP and two patients had 3 hospitalisations for CP. The data shown here include only one hospitalisation per unique person. Note that including all hospitalisations would not make much difference for the results, as between 3 May 2006 and 16 Aug 2009 1013 patients were hospitalised for CP (NCSF members covered with the Carenet database). The adjusted number of hospitalised CP cases for the Belgian population each month, is shown in Figure 7. As already indicated above by the MCD database analyses, CP hospitalisations clearly follow a seasonal pattern in Belgium, with an annual peak around April through June (Figure 7).

Figure 7: Monthly number of hospitalised CP patients in Belgium (June 2006 – July 2009, Carenet).



The number of CP hospitalisations per 100,000 population is highest for children below 2 years of age and differs slightly between boys and girls, depending on age (Figure 8).

Figure 8: Average number of CP hospitalisations per 100,000 in Belgium, stratified by age and by gender. Average over 2007 and 2008, Carenet.



A medical doctor categorised each CP hospitalisation according to the following complication groups (Table 1).

Table 1: Co-morbidities and complication groups for CP hospitalisations.

Abbreviation	Definition
aco	Acute co-morbiditeit (mogelijk primaire oorzaak van hospitalisatie): gastro-enteritis, bronchiolitis, aanslepende bronchitis, otitis, mastoiditis, griep, brandwonde, toxoplasmose, balanitis/fimose, tandabces, hematoom, fractuur, observatie huilen, pneumonie (vermoedelijk niet tgv vzv), commotio cerebri, Henoch-Schönlein, cholecystolithiase, cytomegalovirus, Epstein-Barr virus, lumbalgie
cco	Onderliggende chronische co-morbiditeit: diabetes mellitus, hematologische problemen (maligniteit, G6PDN deficientie met hemolytische crisis), gebruik immunosuppressiva, atopie/allergie, failure-to-thrive, hartafwijkingen, mucoviscidose, quadriparese met refractaire epilepsie, psychomotore retardatie, metabole aandoening, drager van ventriculo-peritoneale shunt
e	Complicaties: veralgemeende encephalitis of onduidelijke cerebrale verwikkelingen zoals convulsies niet nader gespecificeerd
c	Complicaties: cerebellitis
s	Complicaties: sepsis, purpura fulminans, 'necrotiserende varicella'. Ernstige huidinfectie
eh	Complicaties: matige huidinfectie of infectie van de gewrichten of osteo-myelitis: abces met drainage, cellulitis, flegmoon, erysipelas, septische artritis, fasciitis, osteo-myelitis, surinfectie met necrose
h	Complicaties: (bacteriële) huidinfectie/milde surinfectie: impetigo/scarlet fever (scarlatina)/abces zonder drainage/furonkel
p	Complicaties: (broncho)pneumonie/longontsteking/empyeem/pleuritis tgv of post-varicella (als dusdanig weergegeven)
no complication	no complication
other	complication, other than the ones included in the groups already defined

About 40-45% of the hospitalised CP cases had no complication, about 10-15% had a skin infection/mild surinfection (complication group 'h') and another 10-15% had an acute comorbidity which was possibly the primary reason for hospitalisation (complication group 'aco') (Table 2).

Table 2: Hospitalisation rate per 100,000 population, number of and relative proportion of persons hospitalised for chickenpox, by complication group (Carenet).

	Hospitalisation rate		Number of hospitalised CP patients		Relative proportions	
Complication group	2007	2008	2007	2008	2007	2008
No complication	2.84	2.48	300	265	45.0%	40.5%
ACO	0.69	1.02	73	109	11.0%	16.6%
CCO	0.19	0.22	20	24	2.9%	3.6%
E / C / S	0.35	0.29	37	31	5.5%	4.7%
EH	0.51	0.40	54	42	8.1%	6.5%
H	0.88	1.04	93	111	13.9%	17.0%
P	0.32	0.31	34	33	5.1%	5.0%
Other	0.53	0.38	56	40	8.5%	6.1%

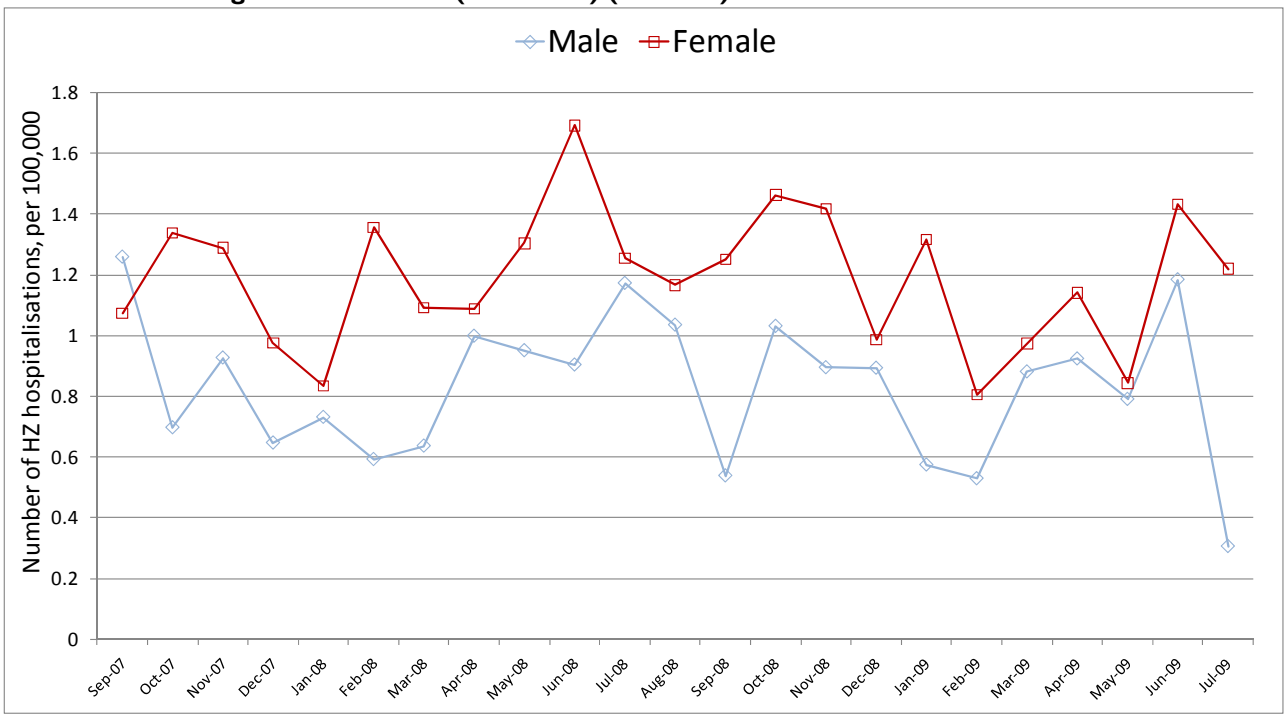
For definitions of the complication groups, see Table 1

Hospitalisations due to HZ (Carenet)

There were 1086 persons hospitalised for HZ in the last two years for which we have data (i.e. 26 Aug 2007 – 25 Aug 2009). For patients who were hospitalised more than once for HZ, only the first hospitalisation was included in the analyses.

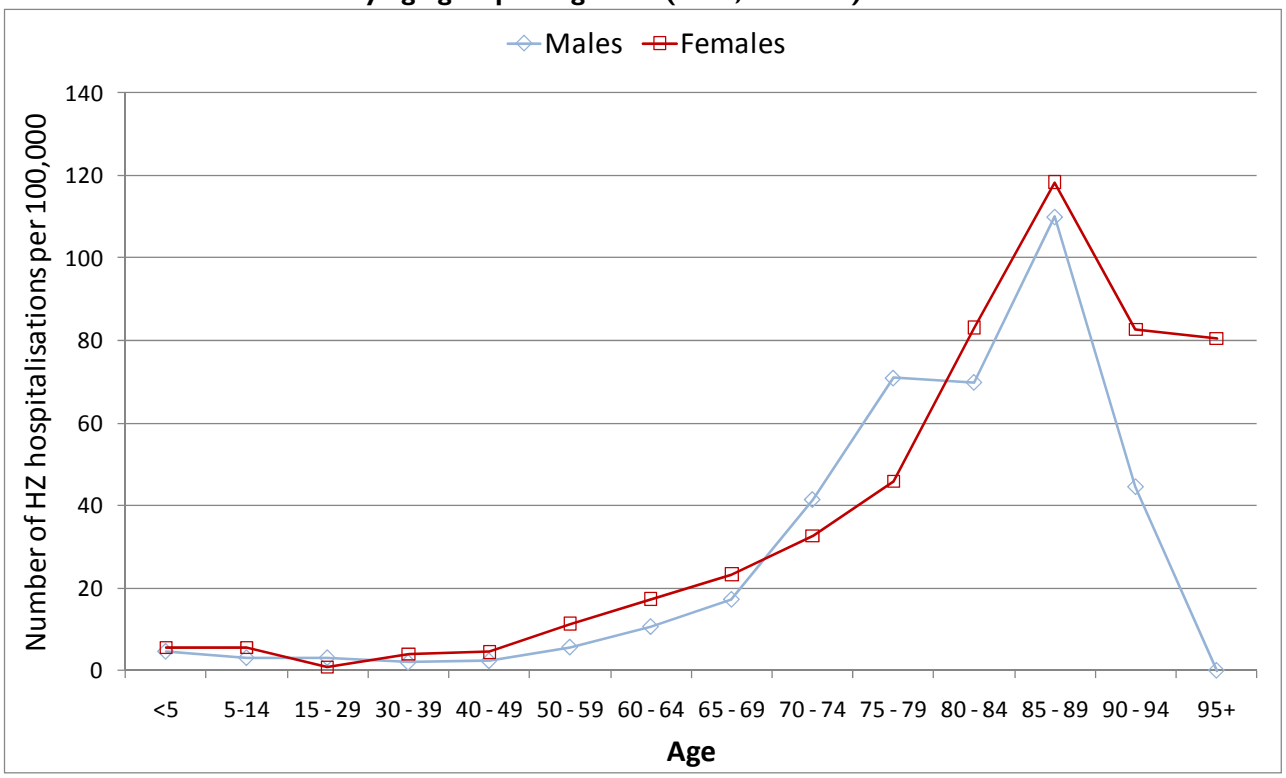
The age-specific monthly hospitalisation rate is shown by gender in Figure 9. It shows that HZ does not have a seasonal pattern, which is in agreement with international data[21].

Figure 9: Number of people hospitalised for HZ per 100,000 population, by gender over time (in months) (Carenet).



The number of hospitalised HZ patients per 100,000 for the Belgian population by age and gender is shown in Figure 10.

Figure 10: Number of people hospitalised for HZ per 100,000 population, stratified by age group and gender (2008, Carenet).

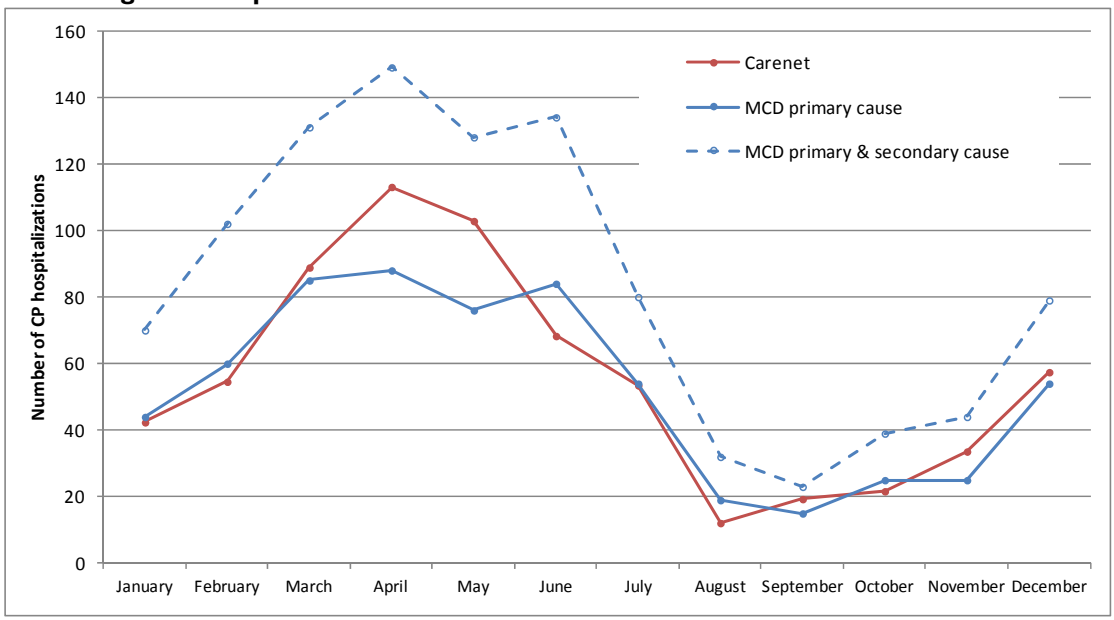


2.2.1.3 Comparison of hospitalisation rate from MCD and Carenet

Comparison of CP hospitalisation rate

The data from MCD and Carenet are both available for 2007 and therefore we will compare the estimated number of hospitalisations in Belgium from these sources by month (Figure 11).

Figure 11: Monthly number of chickenpox hospitalisations in 2007 in Belgium: comparison of estimates based on MCD and Carenet.

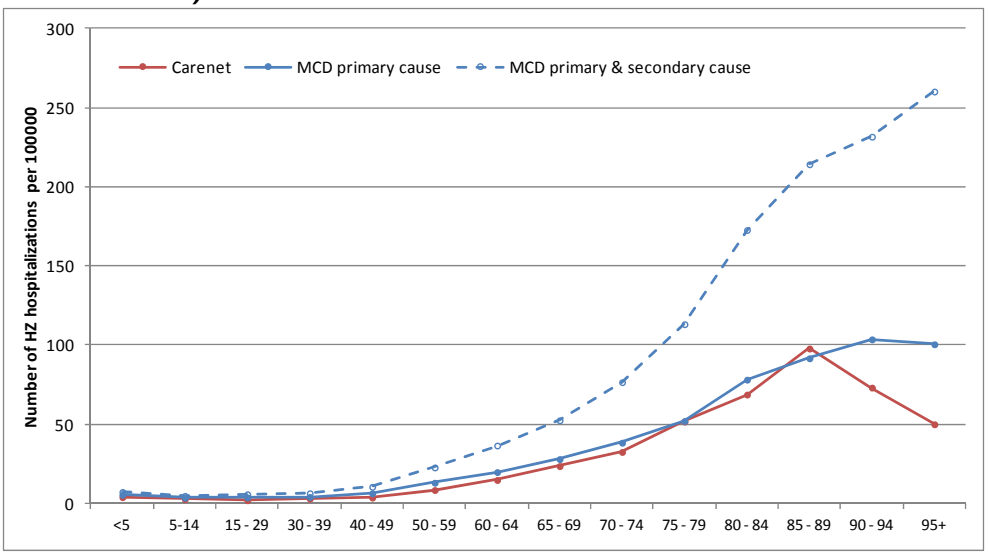


If we include only CP as a primary cause, the number of CP hospitalisations in the MCD are comparable to the number observed in the Carenet database. However, the number of CP hospitalisations, with both primary & secondary cause combined, in MCD are substantially larger. Currently, there is no clear explanation for this difference , other than that diagnostic descriptions in Carenet (for which a distinction between primary and secondary cause cannot be made) may focus, at least in this case, on the main reason for hospitalisation. The trend over the months appear to be similar.

Comparison of HZ hospitalisation rate

The hospitalisation rate for primary cause HZ from MCD is comparable to the hospitalisation rate observed in the Carenet database, but the hospitalisation rates for primary & secondary cause HZ from MCD are again substantially larger. The trend over the months appears to be similar (Figure 12).

Figure 12: Number of HZ hospitalisations per 100,000 by age group: comparison of data obtained from Carenet database (average over 2-year period August 2007-August 2009) and MCD database (data for years 2000-2007 combined).



2.2.1.4 Estimating hospitalisation rates to use as input for CUA

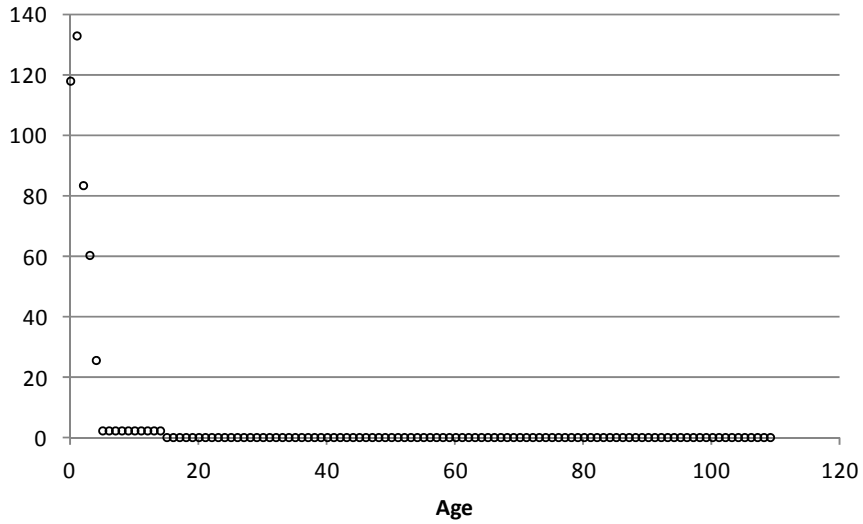
For the CUA (see below), we use the rates obtained from the MCD database, as this database covers the whole of Belgium.

Estimating CP hospitalisation rates to use as input for CUA

Since the age at hospital admission from the MCD database is not very precise, we applied the age distribution of the hospitalisations as recorded in Carenet. Rates were estimated separately for the males and females and for the males and females together (total population), and for primary and primary & secondary diagnosis hospitalisations such that six hospitalisation rates were available for analyses (see below). Because of the small number of CP hospitalisations in persons of age 5 and older, the hospitalisation rate was estimated for the group of 5-14 year olds (being 2.6 hospitalisations per 100,000 population), and the group of age 15 and older (being 0.4 hospitalisations per 100,000 population).

The age-specific hospitalisation rate of primary diagnosis CP is shown in Figure 13 for males and females together, by age.

Figure 13: Estimated average annual number of primary cause CP hospitalisations per 100,000 Belgian population, by age.



Estimating HZ hospitalisation rates to use as input for CUA

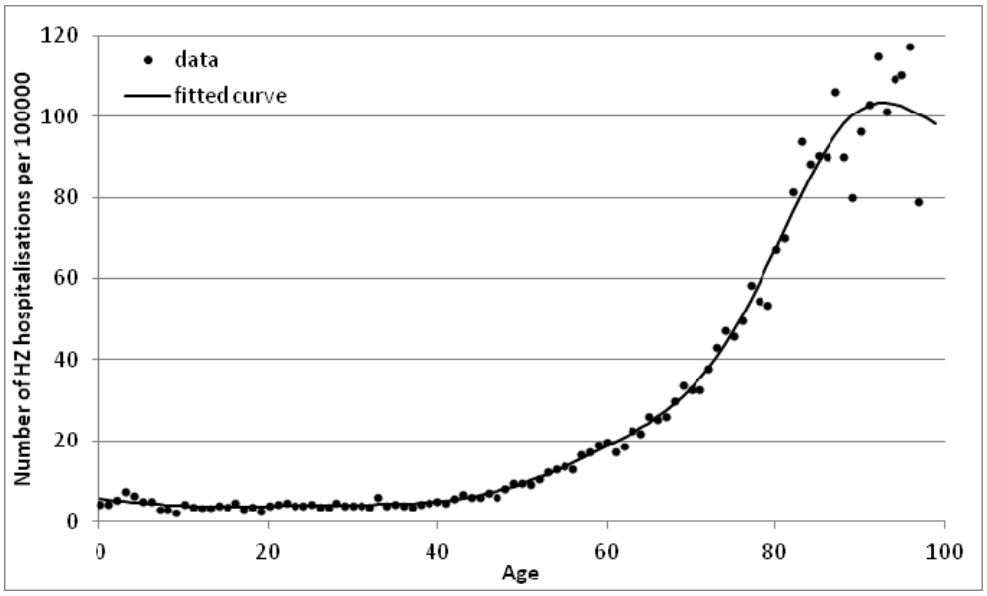
The mean HZ hospitalisation rate by age is estimated by fitting a smooth curve on the MCD data, by age and separately for hospitalisations with HZ as primary diagnosis (Figure 14), and for hospitalisations with HZ as primary or secondary diagnosis. As the HZ hospitalisation rate for the years 2000-2007 is very similar, data for the 8 years were combined. We fitted a general additive model (GAM), which is in our case a non-parametric model in which the parameter term for age of a loglinear regression model[39] is replaced by a function:

$$log\left(\frac{number\ of\ HZ\ hospitalisations_i}{belgian\ population_i}\right) = \alpha + f(age_i)$$

The function f is fitted with a spline (a special function used for smoothing). The dependent variable of this GAM is the number of HZ hospitalisations for each age i (assumed to follow a Poisson distribution), age as covariate, and the Belgian population at each age i as offset. The fitted model is shown including hospitalisations with HZ as primary diagnosis only (Figure 14). Similar models were fitted for any (primary or secondary) diagnosis of HZ, as well as for men and women separately (results not shown).¶

Since the MCD database registers all hospital admissions in Belgium, there is no sample size uncertainty which we should take into account (sample size uncertainty is the uncertainty caused by observing a sample instead of the complete population). Also, we will not look at the year-to-year variation in HZ hospitalisation rate, as we are interested in what happens on average. In other words, in our model, the future age standardised HZ hospitalisation rate is assumed to be, on average, like the age standardised hospitalisation rate observed over the years 2000-2007.

Figure 14: Observed (dots, MCD data, 2000-2007) and estimated (solid line) average annual primary cause HZ hospitalisation rate (per capita) in Belgium, by age.

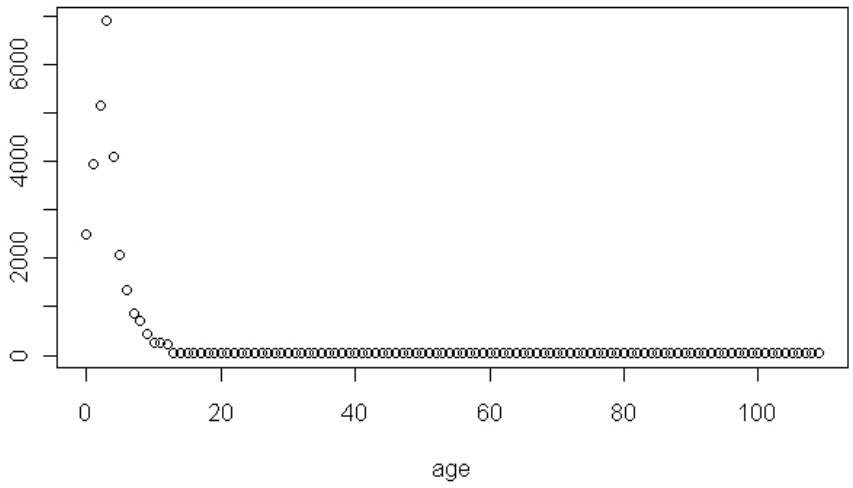


2.2.2 Physician consultations due to CP and HZ

2.2.2.1 Physician consultations due to CP

From the Sentinel General Practitioners we obtained the age-specific number of people who visited a sentinel GP at least once for CP, for years 2006, 2007and 2008, along with the sentinel population per year. As there is no information on the age and gender distribution of the sentinel population, the same age and gender distribution as in the complete Belgian population was assumed. As such, the annual rate by which people visit a sentinel GP at least once could be obtained by age (in years, Figure 15) and by gender. The rates for males and females are similar and are therefore not shown separately. Because of the small number of CP cases of age 12 and older, a single rate at which people visit a GP at least once was estimated for the group of age 12 and older (being 31 CP cases visiting at least once a GP, per 100,000 population).

Figure 15: Age-specific number of CP patients that consult a GP at least once, per 100,000 population.



From the Child & Family survey we obtained information on the different types of medical care that were used by CP patients. We received 108 questionnaires from 13 rural and urban communities in Flanders. Table 3 and Table 4 summarise some basic characteristics of the sample. Note that it was not possible to obtain a representative sample for older age groups with CP who do not require necessarily medical consumption (such as consultations).

Table 3: Age of patients with CP.

Age (years)	Frequency	Relative frequency
0	21	19.44%
1	48	44.44%
2	26	24.07%
3	11	10.19%
4	1	0.93%
5	1	0.93%
TOTAL	**108**	**100%**

Table 4: Highest level of education of respondents.

Education level	Frequency	Relative frequency
secondary vocational education (beroepsonderwijs/enseignement professionel)	12	11.21%
secondary technical education (technisch onderwijs/enseignement technique)	10	9.35%
general secondary education (algemeen secundair onderwijs/enseignement secondaire général)	14	13.08%
secondary education (high school or university) (hoger onderwijs (hogeschool of universiteit)/enseignement secondaire (école supérieure ou université))	71	66.36%
TOTAL	**107**	**100%**

One patient out of the 108 went to hospital (0.93%). Including this patient there were two patients (1.85%) who went to the emergency department.

Table 5 shows the number of times that respondents indicated they consulted a physician.

Table 5: Number of respondents who consulted with a GP, paediatrician or other physician for their chickenpox episode.

	Number of respondents (%) with the following number of visits				
	0	**1**	**2**	**3**	**Total**
GP home visits	91	15	2	0	108
GP consultation	73	29	5	1	108
Paediatrician consultation	89	17	2	0	108
Other physician	0	0	0	0	108

Forty-one of the respondents (37.96%) had no physician consultations, 48 (44.44%) consulted a GP at least once and not a paediatrician, and 19 patients (17.59%) consulted a paediatrician. There were four patients who consulted a paediatrician as well as a GP.

2.2.2.2 Physician consultations due to HZ

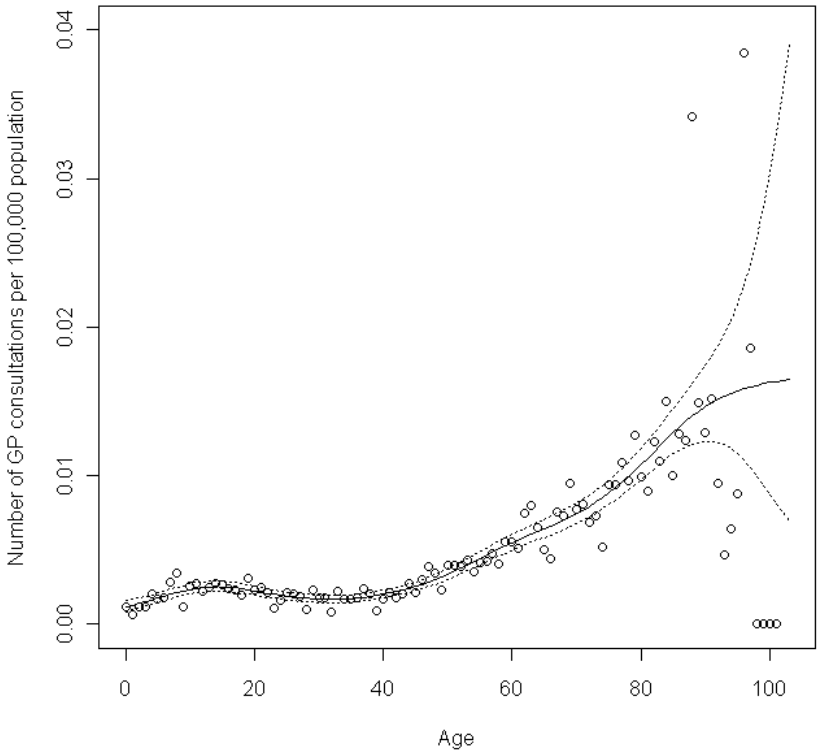
The Sentinel General Practitioners database was used in a similar manner as discussed for CP to obtain the number of patients with at least one GP consultation for HZ. Only patients for whom information on age and/or gender was available, are included (97.8%). As the rates for the 3 different years are very similar, data for the 3 years were combined. The observed rates by age are presented in Figure 16 (open circles). The variation in the observed rate of HZ –related GP visits in the elderly, is due to the very small population size and number of HZ-related GP visits at those ages. Because we are

interested in the average number of HZ-related GP visits, we fitted a general additive model (GAM) to these data, similar to the procedure for the HZ hospitalisation rate (see before):

$$log\left(\frac{number\ of\ HZ\ related\ GP\ visits_i}{sentinel\ population_i}\right) = \alpha + f(age_i)$$

The fitted model and 95% confidence intervals are shown in Figure 16. The same model was fitted for men and women separately (results not shown).

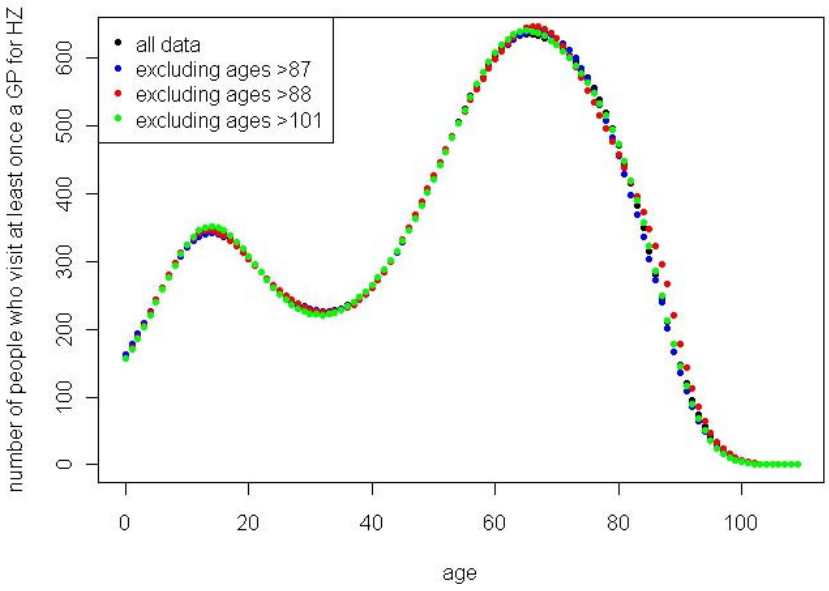
Figure 16: Age-specific number of HZ patients with at least one GP consultation per capita (data SIPH, 2006-2008 (open circles) and fitted mean model with 95% CI (solid and dashed lines)).



Note: As the observed number of GP consultations per 100,000 population for age 102 and 103 was very high (0.15 and 0.30), these points are not presented in this plot because it would make the plot less informative.

Because the number of HZ related visits and the population size is so small for the old ages, one could argue not to use these data and to fit the function only on the ages for which enough information is available, and to assume for the excluded age groups a rate similar to the rate for the oldest age for which the curve was fitted. We explored this issue and found that the choice of the ages to exclude has a strong effect on the shape of the curve for older age groups (not shown). However, this variation has only a negligible impact on the number of HZ-related GP visits for Belgium, because the number of people aged 90 or more is small (Figure 17). Therefore the fitted models on all these data are used as input for our analyses.

Figure 17: Annual number of people in Belgium who visit at least once a GP for HZ, by age: impact of including/excluding scarce data for the oldest ages.



2.2.3 Total number of people with CP and HZ

2.2.3.1 Total number of people with CP

The total number of people with CP infections is derived by calculating the force of infection from seroprevalence data, as shown in the following publications for Belgium: Hens et al[40], Goeyvaerts et al[41], and Shkedy et al[16]. The proportion of the infections that are hospitalised, that have ambulatory care or that do not consume medical care is based on following information:

- NrGP: the estimated number of people with CP who visit a GP at least once (SIPH data);
- the number of people with CP who do not consult any physician, relative to NrGP (41/52=0.79, Child&Family survey);
- the number of people with CP who consult a paediatrician but not a GP, relative to NrGP (15/52=0.29, Child&Family survey);
- NrHOSP: the estimated number of people hospitalised because of CP (MCD);
- the number of hospitalised patients who do not consult a physician in ambulatory care, relative to NrHOSP (10/57=0.18, NCSF sample).

Due to the current pre-vaccination epidemiology, primary VZV infections in over 12 year olds are too sparse in Belgium to provide useful information through a single year survey. Therefore, in view of the severity of primary varicella in teenagers and adults, we assume - rather than estimate - that persons aged older than 12 years will always seek medical care when they incur a primary VZV infection (either by consulting a physician or by being hospitalised).

2.2.3.2 Total number of people with HZ seeking medical care

From the Sentinel System of general practitioners we obtained the number of people who visit at least once a GP for their HZ episode. However, can we assume that everybody with HZ visits at least once a GP?

From our NCSF survey amongst ambulatory HZ patients, we know that 98.5% had at least one GP consultation for their HZ episode, two out of 130 patients went to a dermatologist only, and one person went to an unspecified specialist. However, for the NCSF survey for HZ ambulatory patients a call was made on the internet and magazines, which may have caused a bias towards more severe cases (as they may be more keen on participating). Since the surveyed HZ ambulatory patients might be biased towards more severe HZ, it seems likely that the proportion of HZ ambulatory patients who visit a specialist only, would even be less if milder cases were included. We do not have information on the proportion of HZ patients who do not consult any physician, but we assume that all ambulatory HZ patients visit at least once a GP. For our CUA we therefore assume only the burden in HZ patients seeking medical care to be preventable by HZ vaccination, implying that the vaccine efficacy against HZ cases seeking medical care is assumed to be the same as the vaccine efficacy measured in the Oxman et al[27] trial. It seems a reasonable assumption that people not seeking any type of medical care for their HZ are likely to experience a very small, if not negligible, burden (in terms of costs and QALY loss). Hence, excluding the burden of these people is likely to have a very small impact on the cost-effectiveness of HZ vaccination.

Our NCSF survey amongst hospitalized HZ patients is not likely to be biased, and from this survey we can derive that 10.5% of the hospitalized HZ cases did not visit a GP for their HZ episode (16 out of 153). Most (6.5%) of them instead consulted an unspecified specialist, an ambulatory health care worker, or an emergency department, whereas the remainder (3.9%) were hospitalised directly.

We obtain the total number of people with HZ who seek at least once medical care, by adding to the estimated number of people with HZ who visit at least once a GP, 10.5% of the estimated number of hospitalized HZ patients in Belgium (assuming this proportion to be age independent). As this value of 10.5% is based on a sample of 153 patients, sample size uncertainty is taken into account by assigning a beta distribution with parameters $\alpha = 16$ and $\beta = 153 - 16 = 137$.

2.2.4 Deaths due to CP and HZ

We obtained information from the Flemish death certificates containing codes for CP and HZ in any field for potential cause of death (underlying, immediate, intermediate 1, intermediate 2, additional 1, additional 2, additional 3 cause of death). For the years 1998-2007 there were 193 deaths in Flanders with CP (ICD10: B01) or HZ (ICD10: B02) indicated as a cause of death. At a later stage we also obtained information from the Walloon region (only information available for the years 1998, 1999, 2004 and 2005) and the Brussels region (information available for 1998-2008). In Wallonia, there were 27 such deaths over the 4 years combined, whereas in Brussels there were 61 such deaths over 11 years.

2.2.4.1 Deaths in children

All seven deaths which occurred in children, were coded as potentially due to CP, and not to HZ. Two expert clinicians rated the individual coded information from these seven Flemish death certificates in relation to whether they thought the person in question would still have died if s/he would not have had chickenpox. Both clinicians were in perfect agreement and indicated that five of these seven children died because of CP, whereas they remained unsure about the remaining two children. The age range of the former group, all male, was 1.2 years to 12.8 years, whereas the uncertain group, both female, were aged 1.4 years and 2.3 years. Note that both the death registries of Brussels and Wallonia did not record any death in a child for either chickenpox or zoster.

2.2.4.2 Deaths in adults

In order to gauge which of the adult deaths could be avoided through the avoidance of HZ disease, we eliminated those death certificates for which HZ appeared only as an additional cause of death. Five expert clinicians rated the individual coded information from the 73 remaining Flemish death certificates in relation to whether they thought the person in question would have died if s/he would not have had HZ or chickenpox.

The sample of 73 entries contained 14 entries for which the cause of death was CP, not HZ. Among the CP deaths, the youngest was aged 48 years and the oldest was aged 97 years. Of the 59 entries which had HZ as a cause of death, the youngest was 60.8 years, whereas the oldest was 101.8 years.

We grouped the answers by the number of expert clinicians answering "Yes", "No" or "Unsure" (Table 6). We have also tried to group the answers such that it is clear what the consensus view is, but this remains open for interpretation. Columns E-I in Table 6 could be considered as "Unsure".

Note that after elimination of VZV as an additional cause of death, in Wallonia 3 potential chickenpox deaths and 24 potential HZ deaths in adults (age range 20-102 years) were registered for the four registration years. In Brussels no potential chickenpox deaths and 17 potential HZ deaths in adults (age range 38-96 years) were registered over the period 1998-2008.

Table 6: Opinions of five experts based on Flemish death certificates, about if adults would have died if they would not have had HZ or CP ('yes', 'no' or 'unsure').

		A	B	**A+B="Yes"**	C	D	**C+D="No"**	E	F	G	H	I
	Age group	5"Yes"	4 "Yes" 1"No" or "Unsure"		5"No"	4"No" 1"Yes" or "Unsure"		3"Yes" 2"No"	3"No" 2"Yes"	3"Unsure" 2"Yes"	3"Unsure" 2"No"	4 "Unsure" 1 "No"
HZ	<=59	0	0	**0**	0	0	0	0	0	0	0	0
	60-74	1	2	**3**	0	0	0	0	0	0	1	0
	75-89	4	2	**6**	0	10	10	0	0	0	4	1
	>=90	1	0	1	2	5	7	0	0	0	3	1
CP	<=59	0	1	1	0	2	2	0	0	0	0	0
	60-74	1	0	**1**	0	2	2	1	0	0	0	0
	75-89	1	2	**3**	0	0	0	0	0	0	0	0
	>=90	0	1	**1**	0	1	1	0	0	0	0	0
TOTAL		**8**	**8**	**16**	**2**	**20**	**22**	**1**	**0**	**0**	**8**	**2**

Table 6 (continued) : Opinions of five experts based on Flemish death certificates, about if adults would have died if they would not have had HZ or CP ('yes', 'no' or 'unsure').

	Age group	3 "Yes" 2"Unsure"	3 "No" 2"Unsure"	2 "Yes" 2 "No" 1"Unsure"	2 "Yes" 2"Unsure" 1 "No"	2"No" 2"Unsure" 1 "Yes"	3 "No" 1 "Yes" 1"Unsure"	3"Unsure" 1 "Yes" 1"No"	3"Yes" 1 "No" 1"Unsure"
HZ	<=59	0	0	0	0	0	0	0	0
	60-74	0	0	0	0	1	0	0	0
	75-89	0	5	0	1	2	6	1	0
	>=90	0	3	0	0	1	2	0	0
CP	<=59	0	0	0	0	0	0	0	0
	60-74	0	0	0	0	0	1	0	0
	75-89	0	0	0	0	0	0	0	1
	>=90	0	0	0	0	0	0	0	0
TOTAL		**0**	**8**	**0**	**1**	**4**	**9**	**1**	**1**

Based on the death registry data, the most likely number of CP deaths in Flanders over a period of 10 years is 5 for children younger than age 15, and 5 for adults older than 59 (Table 6, column 'A+B'). This results in CP mortality rates of 0.05 and 0.04 per 100,000 personyears for children younger than age 15 and adults older than 59, respectively.

Death rates used as input for our CUA

CP RELATED DEATHS

As we only have fairly consistent data on deaths caused by CP for Flanders, the number of cases over a 10-year period are very few. That makes it difficult to estimate reliable age-specific mortality rates for all ages. Therefore we will use the CP related case-fatality rates based on the much larger population of England & Wales[42] (Table 7).

Table 7: Age-specific CP mortality rate and case-fatality for England & Wales, taken from Brisson and Edmunds[42].

age	CP mortality rate per 100,000 personyears	Case-fatality (per 100,000 cases)
0-4	0.08	1
5-14	0.02	1
15-44	0.04	9
45-64	0.03	73
65+	0.11	689

HZ RELATED DEATHS

The death rate due to HZ is incorporated in our analyses as follows. The most likely number of deaths for the four age groups is assumed to be the number of deaths for which at least four of the five experts believed the death was due to HZ (i.e. Table 6, column 'A+B'). This is 10 cases in a period of 10 year (1998-2007), hence 1 HZ-related death per year in Flanders. The uncertainty related to if a death registered with HZ as a potential cause, is really caused by HZ, is taking into account through the following two scenario's: A scenario most in favour of vaccination for which we assume the minimum annual number of deaths due to HZ for the four different age groups (see Table 6) to be 0. A scenario least in favour of vaccination, assuming the number of deaths due to HZ derived from the death certificates, is equal to the total number of deaths minus the ones for which at least four of the five experts believed the death was not due to HZ (i.e. Table 6, column 'C+D'). As the death certificates are only for Flanders, not for the complete Belgian population, there is sample size uncertainty. However, Flanders contains about 60% of the Belgian population, so that this sample size uncertainty is small and we therefore will not incorporate this type of uncertainty in our CEA. This also is the case for the uncertainty related to the representativeness of the HZ-related deaths of Flanders, for the Belgian population.

To get the HZ-related death rate, the number of deaths caused by HZ from 1998-2007 is divided by the total population size (Flanders) for the same period for each of the four age groups.

2.2.5 Postherpetic neuralgia (PHN)

The proportion of HZ patients by age who develop PHN is derived from van Hoek et al[43]. They defined PHN as clinical relevant pain (CRP) after 90 days, and estimated the proportion of HZ patients with CRP by age based on seven studies. Different studies used different questionnaires to measure pain associated with HZ, and van Hoek et al[43] defined CRP as pain score of 3 or more on a scale from 1 to 10; or a pain score of 25 or more on a scale from 0 to 100 (depending on which measure of pain the study used). The proportion of HZ patients who develop PHN was estimated to increase exponentially with age (e.g. 5% for people aged 40, and 46% for people aged 90), and to stay constant (68%) for age 96 and older. For more details see van Hoek et al[43]. To get the annual number of people with PHN by age for Belgium, the estimated total number of people with HZ who seek at least once medical care (see before), is multiplied by this age-specific PHN proportion.

2.2.6 HZ related burden-of-illness (BOI)

If we want to use the primary endpoint measured in the SPS trial[27] in our analysis, which is the efficacy of the Zostavax® vaccine against the HZ-related burden-of-illness(see further), we have to have an idea of the HZ-related burden-of-illness (BOI) in the Belgium population.

BOI is a severity-by-duration measure of the total pain and discomfort in a population, associated with HZ. It is based on the ZBPI (Zoster Brief Pain Inventory) severity-duration measure defined by Coplan et al[44]. This measure is defined as the area under the curve of HZ pain (answer to the 'worst pain' question in the Zoster Brief Pain Inventory), plotted against time (number of days with HZ pain starting from rash onset until the HZ pain resolved)[44]. In the SPS trial[27] however, instead of the ZBPI severity-duration measure, a severity-of-illness score was obtained (SOIS, note that this is not the SOI of the APrDRG classification system),which measures duration of HZ pain for a maximum of 182 days after rash onset. Hence, subjects could have SOIS ranging from 0 to 1820 (a SOIS of 0 representing no HZ pain, and a SOIS of 1820 representing 182 days of maximum pain, i.e. 182 times score ‘10’). The BOI then represents the average SOIS among all subjects in a population, with a SOIS of 0 for all subjects in whomHZ did not develop during the 182 days (see also Chang et al[45]).

How can we obtain HZ related BOI for the Belgium population?

Ideally, we should setup a prospective study following a representative sample of patients in Belgium throughout their HZ episode, questioning them about their pain (cfr. the prospective studies of Scott et al[34] and Drolet et al[7, 46, 47]). Unfortunately, within the timeframe for conducting the CUA which is the subject of this report, it was not possible to conduct such a study. Therefore, BOI for the Belgian population was decided to be estimated as follows:

From our NCSF survey amongst hospitalized HZ patients, we can derive average SOIS for a HZ case in hospitalized settings. The same could be done for the NCSF survey amongst ambulatory HZ patients, but, as mentioned before, there is a likely bias towards respondents having experienced more severe HZ. Therefore, we will obtain the SOIS for an average ambulatory HZ patient indirectly, based on SOIS measured in comparable populations as the Belgian population (see further). Characteristics of the respondents of the NCSF surveys are described on p.39 (survey in hospitalized HZ patients) and p.44 (survey in ambulatory HZ patients).

2.2.6.1 Estimating SOIS for a hospitalised HZ patient

The SOIS of the hospitalised HZ patients from the NCSF survey is obtained by multiplying the answer to the worst pain question in our survey, by the duration of the HZ episode. As such it differs from the SOIS as measured in the SPS trial, as the worst pain question in the NCSF survey asked retrospectively about the worst pain experienced because of having HZ. The SOIS of the hospitalised HZ patients from the NCSF survey is exponentially distributed (@Risk). The expected value of this exponential distribution is modelled as a function of age. A model adding gender as a covariate and the interaction between age and gender was not found to be better (AIC value=2159 for the model with age only, which is smaller than the AIC value=2162 for the model including gender). Data exploration indicated that a linear function provided a satisfactory description of the relationship between SOIS and age:

$$E(SOIShosp) = \beta_0 + \beta_1 age$$

Parameter estimates are provided in Table 8, the fitted curve is shown in

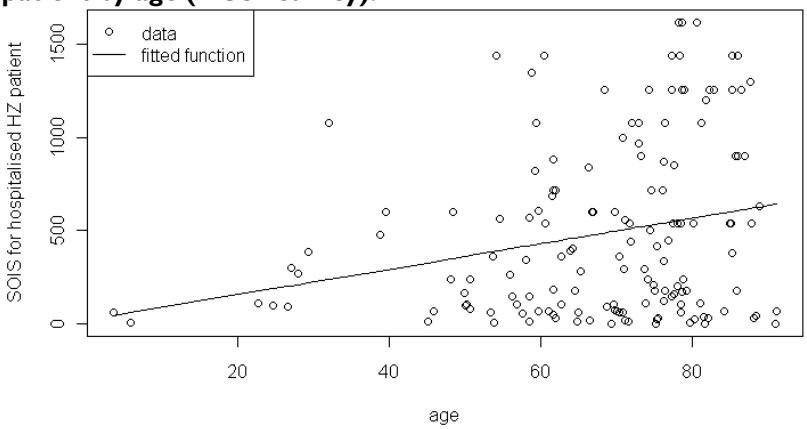
Variable	Estimated value	Estimated standard error
β_0	19.762549	39.026881
β_1	6.842568	0.870012

Figure **18**.

Table 8: Parameter estimates for SOIS related to hospitalised HZ patients, as a function of age.

Variable	Estimated value	Estimated standard error
β_0	19.762549	39.026881
β_1	6.842568	0.870012

Figure 18: Data and fitted curve for SOIS related to a hospitalised HZ patient by age (NCSF survey).



Adding PHN as a covariate (1=PHN, 0=HZ without PHN) improves the model (AIC = 2064). PHN is defined as having a pain score of 3 or more on the worst pain question in the NCSF survey (hence, answered retrospectively), and being sick for more than 90 days. The model becomes:

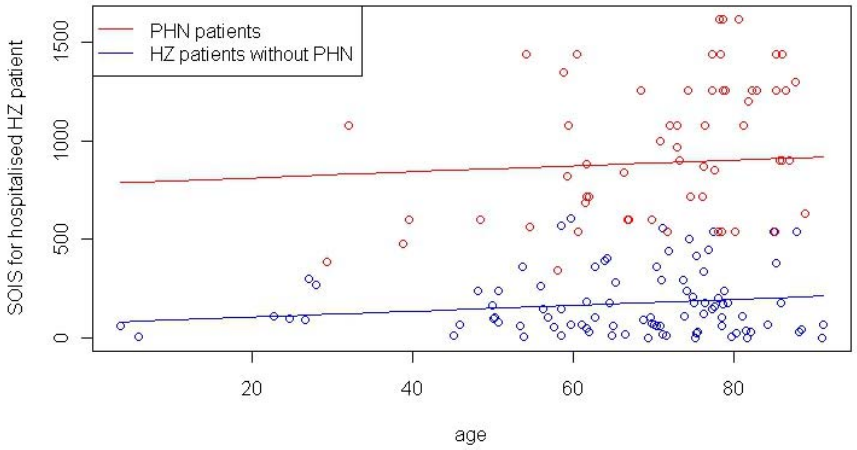
$$E(SOIShosp) = \beta_0 + \beta_1 age + \beta_2 PHN$$

Parameter estimates are provided in Table 9, the fitted curves are shown in Figure 19.

Table 9: Parameter estimates for SOIS related to hospitalised HZ patients, as a function of age and having PHN (yes/no).

Variable	Estimated value	Estimated standard error
β_0	76.607674	59.6523227
β_1	1.485659	0.9716209
β_2	707.903338	109.7780272

Figure 19: Data (open circles) and fitted curves for SOIS related to a hospitalised HZ patient by age and having PHN (yes/no) (NCSF survey).



There is no different relationship between SOIS and age for patients who would or would not have been excluded from the SPS trial based on the exclusion criteria (see p.43). The fitted curves (i.e. the estimated parameters of the curves) are used as input for our CUA.

2.2.6.2 Estimating SOIS for an ambulatory HZ patient

Only data on SOIS for an average HZ patient, not for an ambulatory HZ patient is available from the literature. Therefore we will obtain an estimate for SOIS for an ambulatory HZ patient in two steps: 1) estimating SOIS for an average HZ patient by age, based on literature, 2) estimating SOIS for an ambulatory HZ patient based on SOIS for an average HZ patient (1), for a hospitalised HZ patient (p.30) and the proportion of HZ patients hospitalised versus ambulatory treatment (p.25). The same approach is taken for the estimation of SOIS by age for ambulatory patients with PHN, without PHN and immunocompetent patients.

SOIS for an average HZ patient

Besides the placebo group of the SPS trial[27], SOIS was measured for HZ patients seeking medical care by Scott et al[34] and Drolet et al[46] (Table 10).

Table 10: Average (median) [min-max] SOIS for an average HZ case, by age.

	Scott et al[34], calculated using the raw data	Oxman et al[27] (placebo group)	Drolet et al[46]
Age 60-69	36.9 (9.2)[4-192.5] (n=8)	134 (n=334)	250 (n=78)
Age 70 and older	31.6 (9.4)[0-176] (n=21)	225 (n=308)	331 (n=82)

How can we explain the huge differences between the studies listed in Table 10?

We would expect Oxman et al[27] underestimated the average SOIS for an average HZ patient seeking medical care, because they started from subjects without HZ, monitoring them actively for HZ-like symptoms, so that they likely included in their average SOIS the burden of HZ patients who normally would not seek medical care for their HZ. The two other studies only assessed SOIS in HZ patients seeking medical care. Therefore, it is also unexpected that the average SOIS measured in the Scott et al[34] population is so much lower than what is seen in the Oxman et al[27] population. But, Oxman et al[27] used strong exclusion criteria, they excluded for instance immunocompromised patients. It is unclear whether immunocompromised patients are expected to have generally a higher or a lower average HZ-related SOIS compared to non-immunocompromised patients.

The difference between the SOIS observed by Scott et al[34] and Drolet et al[46] is also reflected in a difference in the percentage of patients with PHN (defined as having a pain score of 3 or more persisting 3 months after rash onset) among the subjects included in the study differ: 22% in Drolet et al[46] compared to 10.5% in Scott et al[34] in patients aged 50 or older. The difference is difficult to explain:

First of all, it is not possible to assess whether this difference is significant, because no confidence intervals for the age-specific estimates of SOIS for an average HZ patient from Drolet et al[34] are published. Also, the sample size of the Scott study is quite small (especially for the older ages), and the variation in SOIS between individuals becomes increasingly larger for older ages (see Figure 20). However, Drolet et al[7] did publish 95% confidence intervals for the non-PHN cases (Table 11), and the lower ends of these confidence intervals are still higher than the maximum SOIS observed by Scott and colleagues in HZ patients not having PHN (max SOIS patients 61-70 yrs: < 60, max SOIS patients 70 or older: < 80, see Figure 20).

Secondly, the difference is difficult to explain, because the methodology of the two studies is very comparable. Possible explanations for the higher SOIS observed by Drolet et al[46] compared to Scott et al[34] are 1) in the Drolet et al[46] study, 11% of the subjects were recruited by specialists (the remainder by GP's, personal communication M. Drolet, 2010), whereas in the Scott et al study[34] all subjects were recruited by GP's; and 2) in Drolet et al[46] recruitment occurred within 14 days after rash onset, and in Scott et al study[34] within 7 days after rash onset. But, there are also some reasons why one could expect the SOIS of Drolet et al[46] to be lower than the SOIS obtained by Scott et al[34]: 1) in the Drolet et al[46] study almost 90% of the HZ patients received antiviral medication, compared to about 79% in the Scott et al study[34]; and 2) Drolet et al[46] used the 'modified scale' from Coplan et al[44], assuming pain scores of <3 after 30 days to be 0, whereas the values given in Table 10 for the Scott et al study[34] are obtained without making that assumption.

Possibly, the difference is SOIS results from cultural differences between the populations that were followed: Scott et al followed HZ patients in East London (UK), whereas Drolet et al followed HZ patients in Canada.

As it is not clear from the available information which of the studies is most representative for the Belgian population, one analysis will be done using the SOIS of Scott et al[34], and another will be done using the SOIS of Drolet et al[46].

SOIS by age group and having PHN (yes or no) from the Drolet et al study were taken from their publication[7] (Table 10 and Table 11). PHN was defined as having a pain score of 3 or more on the worst pain question, persisting or appearing more than 90 days after rash onset[7].

Table 11: HZ SOIS experienced by immunocompetent subjects who developed PHN during study follow-up compared to those who did not. Table retrieved from Drolet et al[7].

	PHN (n=63)	no PHN (n=198)
49-60 yrs	542.1 (448.1- 636.1)	126.5 (85.1- 167.9)
61-70 yrs	733.4 (642.9- 824.0)	180.7 (132.8- 228.6)
>70 yrs	787.5 (719.8- 855.3)	149.6 (99.6- 199.5)

With the Scott et al[34] data available, we could estimate SOIS by age (in years), gender, by having PHN (yes or no) and by being immunocompetent (yes or no). The SOIS for each patient from Scott et al[34] is calculated similar as in Oxman et al[27]: for every patient, a pain score (answer to the worst pain question of the ZBPI) was measured at baseline, and four weeks, three months and six months after study initiation. By plotting the pain scores over time, the area under such a curve provides the total SOIS of a patient based on the first 6 months after rash onset. The pain score was assumed to change linearly between the time points at which pain was measured. The data of Scott et al[34] contained patients who withdrew consent from the study or were lost to follow up. The SOIS score for such patients are therefore right censored.

Based on an analysis using @Risk, it was estimated that the SOIS of the uncensored cases follows a lognormal distribution. The expected SOIS of each patient is modelled to change exponentially with age, and to be different for men and women:

$$SOIS = e^{\beta_0+\beta_1 Age+\beta_2 Gender+\frac{\sigma^2}{2}}$$

with β_0 ,β_1 ,β_2 and σ being the parameters to estimate, and $Gender$ being 1 for women, and 0 for men. The estimation of the parameters was conducted using maximum likelihood (ML) methods in R which is done using Newton-type optimisation methods. The standard deviation of the parameter estimates was estimated by the hessian of the maximisation method. The right-censoring was taken into account as follows:

If X follows a distribution $f(X;\boldsymbol{\theta})$ where $\boldsymbol{\theta}$ is a list of parameters and there is no censoring, the ML estimates of $\boldsymbol{\theta}$ is found by maximizing:

$$L = \prod_{i=1}^{n} f_X(x_i;\boldsymbol{\theta})$$

where $f_X(x_i;\boldsymbol{\theta})$ is the density function of X evaluated at the point x_i given $\boldsymbol{\theta}$. If an observed value x_j is right censored, we know that the true value of the observation is at least x_j. This information is added to the likelihood function as $1 - F_X(x_j;\boldsymbol{\theta})$, where $F_X(x_j;\boldsymbol{\theta})$ is the distribution function of X at the point x_j given $\boldsymbol{\theta}$. The likelihood function that should be estimated then becomes:

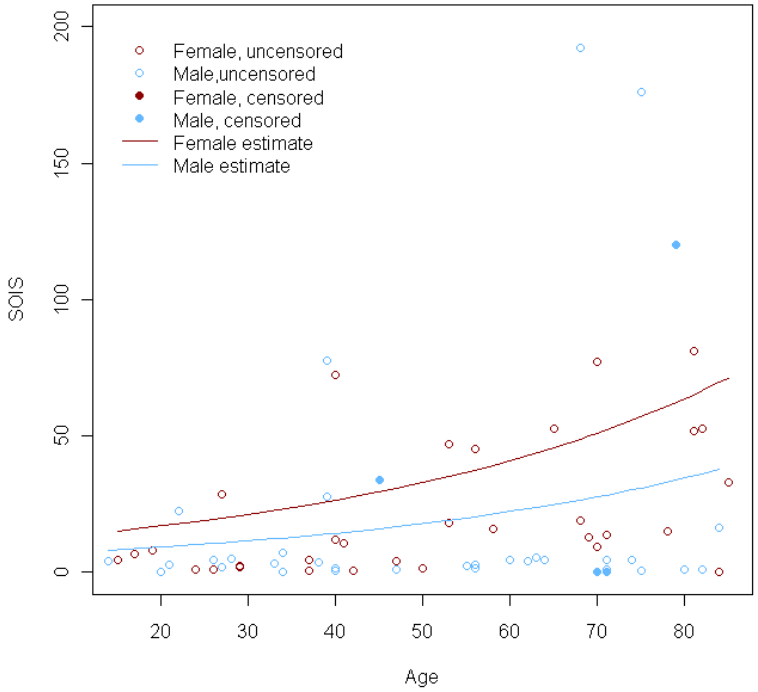
$$L = \prod_{uncensored} f_X(x_i;\boldsymbol{\theta}) \prod_{censored} 1 - F_X(x_j;\boldsymbol{\theta})$$

The parameter estimates are presented in Table 12, the Scott et al[34] data and the fitted function are presented in Figure 20.

Table 12: Parameter estimates for SOIS related to an average HZ episode, as a function of age and gender.

Variable	Estimated value	Estimated standard error
β_0	0.42821191	0.5591568
β_1	0.02206536	0.009525884
β_2	0.61040432	0.4021205
σ	1.64316565	0.1446615

Figure 20: Scott et al (2006) data (points) and estimated function (lines) of SOIS by age and gender



From Figure 20 we see the SOIS is estimated on average higher for women compared to men, and increases exponentially with age. The reason why the estimated SOIS (solid lines in Figure 20) seems to lie slightly above a substantial part of the data points, is because censoring was taken into account. I.e. the plotted censored points (filled circles in Figure 20) show the minimum SOIS for these patients, and likely the 'real' SOIS is higher for them, pulling the estimated SOIS upwards. The fitted curves (i.e. the estimated parameters of the curves) are used as input for our CUA.

We also estimated SOIS by age and gender for the subjects without PHN (results Figure 21), and for the immunocompetent patients (as defined by Scott et al[34]) only (results see Figure 22). The analysis for the subjects without PHN also excluded all right-censored cases, as for these cases it was not possible to determine if they developed PHN yes or no. PHN was defined as a score of 3 or more 90 days after disease onset. Separate analyses were done rather than adding PHN (yes or no) and immunocompromised (yes or no) as covariates, as only a very small proportion of subjects had PHN (n=5) and/or was immunocompromised (n=9). As expected, excluding the PHN cases and immunocompromised patients decreases the median SOIS by age.

Figure 21: Scott et al (2006) data (points) and estimated function (lines) of SOIS related to an average HZ episode (but not PHN), by age and gender.

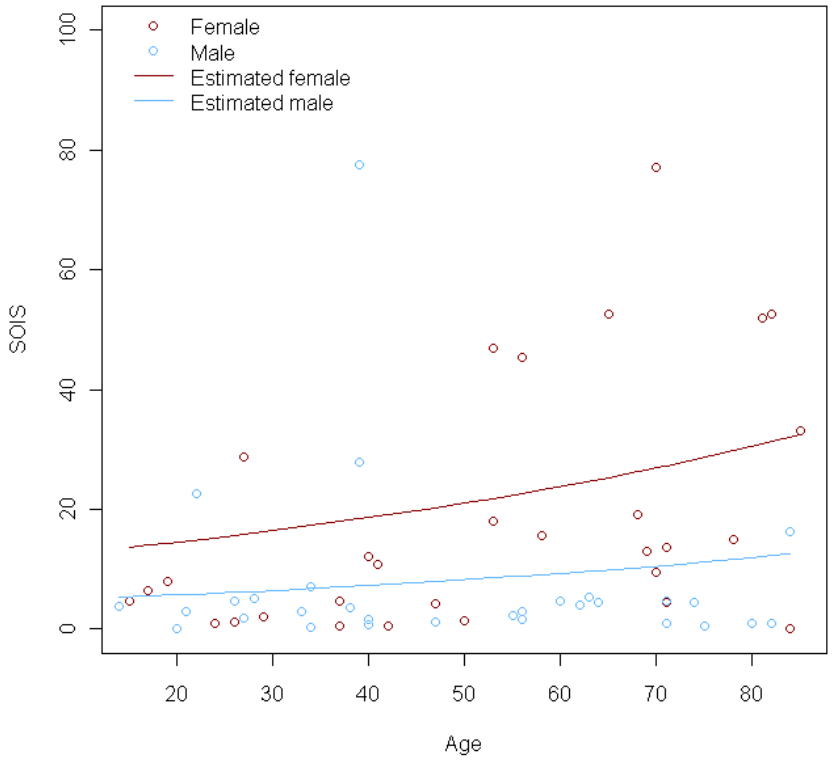
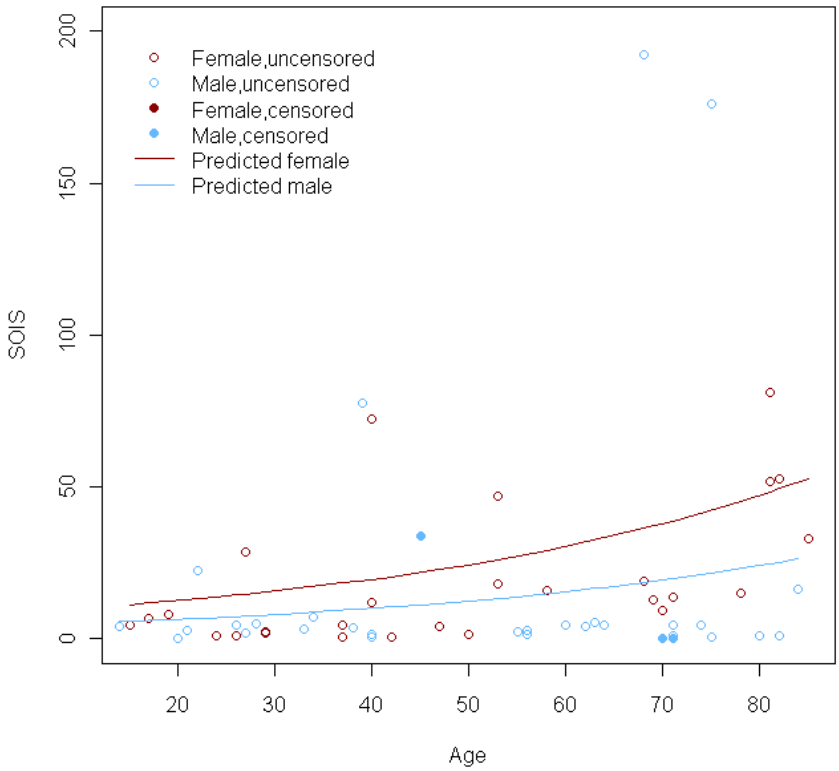


Figure 22: Scott et al (2006) data (points) and estimated function (lines) of SOIS related to an average HZ episode in immunocompetent subjects, by age and gender.



Because Scott et al[34] data contain too few PHN cases to get a reliable estimate for the average SOIS for patients with PHN, we assume the same proportional increase in SOIS for PHN cases compared to non-PHN cases, as reported by Drolet et al[7], i.e. 4.285, 4.059 and 5.264 times higher for ages 49-60, 61-70 and >70 years respectively. For ages <49, we assume the same value as for ages 49-60 yrs. As we do not have access to the raw data from Drolet et al[7], uncertainty could not be taken into account appropriately.

SOIS for an ambulatory HZ patient

From:

$$SOIS_i = propHZhosp_i * SOIShosp_i + propHZamb_i * SOISamb_i$$

for each age i, we can derive that:

$$SOISamb_i = \frac{SOIS_i - propHZhosp_i * SOIShosp_i}{propHZamb_i}$$

With SOIS = SOIS for an average HZ patient; SOIShosp and SOISamb = SOIS for a hospitalised and ambulatory HZ patient respectively; propHZhosp and propHZamb = proportion of HZ patients being hospitalised and being treated ambulatory respectively. The same formula is used for the estimation of $SOISamb_i$ for patients with and without PHN, and for immunocompetent patients, by plugging in the appropriate estimates for SOIS (Figure 21 and Figure 22), SOIShosp (paragraph 0 p.30), propHZhosp (Table 17 and Table 18) and propHZamb (Table 30) for each of these specific groups of HZ patients.

2.2.6.3 Estimating HZ related burden-of-illness (BOI) for Belgium

With the estimated SOIS by age (and gender), we can calculate the HZ related BOI for Belgium as follows:

for each age i:

$$BOI_i = \frac{propHZhosp_i * SOIShosp_i + propHZamb_i * SOISamb_i}{total\ population_i}$$

With $total\ population_i$, the number of people in Belgium with age i, for the other abbreviations, see above ('SOIS for an ambulatory HZ patient').

2.3 COSTS RELATED TO CHICKENPOX AND HERPES ZOSTER

Costs related to CP and HZ are derived from the NCSF surveys.

2.3.1 Costs for people hospitalised for CP and HZ

2.3.1.1 Costs for people hospitalised for CP

Fifty-seven patients who were hospitalised between 9/11/2007 and 27/07/2009 completed the NCSF questionnaire. One of these patients was not hospitalised for varicella and was therefore removed, resulting in a sample size of 56 for the analysis. The sample did not differ significantly from the total Carenet dataset with respect to the distribution of CP cases by age, gender, month, length of stay and complication group. The sample however did not include very old patients who were hospitalised and patients who stayed in the hospital for more than 14 days. Also, no patients from complication group 'cco' were included. The majority of the questionnaires was completed by the mother of the sick child (79%), the remaining questionnaires were completed by the father or the person with CP. For 73% of the respondents the highest level of education was higher education ('hogeschool/école supérieure' or university). Patients stayed in the hospital on average for 5.071 days (median=4, range=2-13). Patients were sick on average for 13.7 days (median=13, range=4-49). 72% of the patients still had scars because of CP.

The direct medical costs are presented in Table 13 and include costs for hospital stay, consultations, medical procedures and medication (for details see Appendix 1: costs related to questions 7-18). The total cost of hospitalization for each patient is recalculated, by replacing the billed ('gefactureerde') cost of stay (as reported in Carenet), by the hospital- and period-specific 100% cost per stay in that hospital multiplied by the number of days the patient stayed in the hospital. This is because in Belgium, hospital per diem costs are covered by 2 distinct systems of public health funding, and the billed ('gefactureerde') per diem cost is only roughly about 20% of the total per diem cost (for details see also KCE report 102, page 37, http://www.kce.fgov.be/index_nl.aspx?SGREF=12647&CREF=12637, latest access 26 aug 2010).

Table 13: Summary costs paid by the National Health care System ('NHS'), co-payments ('Other') and total cost ('Total') for people hospitalised for CP: cost of the hospital stay ('Hospital') and direct medical costs outside the hospital ('Non hospital').

	Hospital			Non hospital		
Summary statistics	**Other (€)**	**NHS (€)**	**Total (€)**	**Other (€)**	**NHS (€)**	**Total (€)**
Min	24.14	1011.27	1074.22	0	0	0
1st Quartile	109.80	1815.49	1970.92	11.88	21.31	33.71
Median	157.30	2192.65	2386.04	19.66	42.62	66.34
Mean	226.20	2561.47	2787.67	26.98	64.53	91.50
3rd Quartile	275.30	3150.20	3515.74	31.85	77.49	118.50
Max	1050.00	5576.09	6057.51	157.5	373.60	531.0
Standard deviation	198.48	1168.89	1254.01	28.02	72.28	96.33

There is a strong positive correlation between duration of stay in the hospital and total direct medical costs, and a less strong, but still positive relationship between total direct medical costs and the number of days sick (results not shown). Total direct medical costs differ slightly between the various complication groups (Table 14). However, it should be noted that sample sizes are too small for a formal comparison in this respect, since the sample was drawn to estimate the costs of an average CP hospitalised case, and not to estimate the costs of each of the complications.

Table 14: Total direct medical cost (€) of a hospitalised CP case, by complication group.

Complication group	Number of respondents	Mean	Median	Standard deviation
ACO	9	2590.677	2405.097	941.0713
CCO	0			
E / C / S	2	4515.839	4515.839	1268.944
EH	4	5713.474	5700.868	387.4651
H	11	2764.776	2490.238	1353.212
P	1	4360.74	4360.74	
Other	5	3108.745	3749.08	1060.546
No complications	24	2321.449	2277.182	691.4047

For definitions of the complication groups, see Table 1

A lognormal distribution provides a good fit for the total direct medical cost for CP (@Risk). The expected value of the cost can be calculated with the following formula:

$$e^{\mu+\frac{\sigma^2}{2}} \qquad (1)$$

The parameters estimated for this function are shown in Table 15.

Table 15: Parameter estimates for total direct medical cost of a hospitalised CP case (NCSF survey).

Parameter	Estimate	Standard error
μ	7.877395	0.05505996
σ	0.412031	0.03893327

The personal direct costs for transport, non-reimbursed care products and medication are presented in Table 16. Three of the patients had paid help at their house (for instance a babysitter) of which the costs were €10, €50 and €100.

Table 16: Total direct personal costs of a hospitalised CP case: number and percentage of respondents that indicated the different cost categories.

	Transport		Care products		Medication	
Cost	nr	perc	nr	perc	nr	perc
Less than €20	18	32.14%	40	71.43%	32	57.14%
Between €20 and €50	22	39.28	5	8.93%	4	7.14%
More than €50	16	28.57%	6	10.71%	3	5.36%
Did not respond	0	0.00%	5	7.14	17	25.00%

Only the not reimbursed care products and medication are considered here. nr=number of respondents, perc=percentage of respondents

Work loss due to a hospitalised CP case was calculated as the number of days that parents / patients were not able to work, multiplied by the daily salary. The average daily salary of a blue collar worker ('arbeider') is €120.175, and that of a white collar worker ('bediende') is €178.068 ('Het absenteïsme in België 2006' ZebraZone European Research & Service Center, costs are inflated to 2007). No salaries are available for self-employed people ('zelfstandigen') from this source and therefore white collar worker's

salary are used as an estimate. Forty out of the 56 respondents interrupted their working activities because their child was hospitalised for CP. These 40 respondents missed work for a median four days (mean= 6, maximum = 30). The median cost related to this work loss is €447.4, the mean €561.7 and the maximum €2493. Four adults (>18 years of age) were hospitalised for CP, and two of them reported they could not work for 10 and 30 days, respectively (giving an associated work loss cost of €1781 and €3605, respectively).

2.3.1.2 Costs for people hospitalised for HZ

The NCSF questionnaire was completed by 153 patients who were hospitalised between 26/01/2008 and 25/08/2009. The sample did not differ significantly from the Carenet data set with respect to distribution of hospitalised HZ patients by gender and age. The sample however includes proportionally fewer patients aged older than 80, possibly because these patients are more likely to have died in the meanwhile, or are not able to respond to the questionnaires. Also, the sample did not include patients who stayed for a very long time (more than 50 days) in the hospital.

The majority of the questionnaires was completed by the person who was hospitalised for HZ (75%), the remaining questionnaires were completed by the partner or the child of the person who was hospitalised for HZ, or by someone else. For 25% of the respondents the highest level of education was higher education ('hogeschool/école supérieure' or university), for 22% of the respondents primary school and for another 22% of the respondents secondary vocational education ('beroepsonderwijs/enseignement professionel'. Patients stayed on average ten days in hospital (mean=10, median=7, range=1-68). Patients were sick on average for 124 days (mean=124.2, median=60, range=3-892). However, 32% of these patients were still sick because of HZ at the moment they completed the questionnaire, for 83% of the patients it was the first time they had HZ. About half (49%) of the patients reported they suffered from another disease during their HZ episode. A clinician went through the responses of the survey to asses if the patients would have been excluded from the Oxman et al[27] trial based on the conditions of the immune system.

The highest proportion of hospitalized HZ patients who would have been excluded, are younger than 60, or older than 70 (Table 17). The proportion of hospitalised HZ patients with PHN (defined as having a pain score of 3 or more on the worst pain question, and being sick for more than 90 days) is presented in Table 18.

Table 17: Hospitalised HZ patients included in the NCSF survey by age group: patients that would have been excluded from the Oxman et al[27] trial based on the conditions of the immune system ('excluded'), all patients, and the proportion of excluded patients from all patients.

Age	Excluded	All	excluded/all
<60	17	27	63%
60-69	11	27	41%
70-79	30	50	60%
80 and older	18	32	56%
ages 60 and older	59	109	54%
all ages	76	136	56%

Table 18: Hospitalised HZ patients included in the NCSF survey by age group, and having PHN.

Age	PHN	No PHN	PHN/all
<60	11	27	28.95%
60-69	11	17	39.29%
70-79	21	34	38.18%
80 and older	16	14	53.33%

Table 19 presents the pain the persons with HZ experienced, based on a pain scale from 1 (no pain) to 10 (worst pain imaginable) derived from the Zoster Brief Pain Inventory. The direct medical costs (covering the same costs as described for CP, including the correction for 100% per diem cost) are presented in Table 20.

Table 19: Pain experienced by people hospitalised for HZ. Worst, least and average pain during their entire HZ period on a scale from 1 (no pain) to 10 (worst pain imaginable).

Pain score	Worst pain		Least pain		Average pain	
	nr	perc	nr	perc	nr	perc
0	5	3.29%	20	13.25%	5	3.29%
1	1	0.66%	15	9.93%	9	5.92%
2	5	3.29%	23	15.23%	8	5.26%
3	4	2.63%	27	17.88%	14	9.21%
4	2	1.32%	19	12.85%	15	9.87%
5	5	3.29%	20	13.25%	29	19.08%
6	9	5.92%	6	3.97%	24	15.79%
7	14	9.21%	11	7.29%	25	16.45%
8	35	23.03%	9	5.96%	17	11.18%
9	24	15.79%	1	0.66%	5	3.29%
10	47	30.92%	0	0%	1	0.66%

nr=number of respondents, perc=percentage of respondents

Table 20: Summary of costs paid by the National Health care System ('NHS'), co-payments ('other') and total cost ('total') for people hospitalised for HZ: cost of the hospital stay ('Hospital') and direct medical costs outside the hospital ('Non hospital').

Summary statistics	Hospital other (€)	Hospital NHS (€)	Hospital total (€)	Non hospital other (€)	Non hospital NHS (€)	Non hospital TOT (€)
Min	19.92	603.02	725.22	0	0	0
1st Quartile	110.90	2811.72	3030.84	13.08	56.37	75.06
Median	205.70	3871.75	4135.58	35.03	175.40	214.60
Mean	283.30	5154.30	5437.63	100.10	355.40	455.50
3rd Quartile	376.40	6134.79	6414.81	80.52	414.10	488.40
Max	1646.00	27539.50	28808.40	2510.00	3908.00	4765.00
Standard deviation	261.0745	4148.649	4298.825	240.0517	530.4982	704.6844

There is no clear relationship between total direct medical cost and age of the patient, but the extreme high costs are all for patients older than 70 (results not shown). The longer the stay in the hospital, the higher the total direct medical costs, and the relationship between numbers of day sick and the total direct medical costs is not as strong (results not shown).

One third of the patients from the NCSF survey were still sick by the time the sample was taken and therefore their total direct medical costs are right censored. For the rest of this discussion we will refer to total direct medical costs as 'costs'. We used @Risk to fit distributions to the uncensored costs and the log-logistic distribution provided the best fit to the data.

Next, we model the direct medical cost of a hospitalized HZ patient as a function of SOIS. By doing so, we can investigate the impact of the vaccine on HZ related costs when considering its efficacy against BOI. In that scenario, we take into account not only that the vaccine decreases the number of HZ cases, but also that vaccination decreases the severity and duration of pain in HZ cases (see further). From our estimated average cost by SOIS, we can read easily how the decrease in BOI (SOIS for an average HZ case) caused by the vaccine, is reflected in a decrease in cost for an average HZ case. Similarly, we can read how the SOIS scores for immunocompetent HZ cases (Figure 22), and for HZ cases without PHN (Figure 21), result in higher/lower costs for these groups.

To obtain cost as a function of SOIS, the expected value (the mean) of the log-logistic distribution for cost is replaced by a function of SOIS. In short, if a random variable X follows a log-logistic distribution, we know that $ln(X)$ follows a logistic distribution with parameters μ and s such that the expected value of $ln(X)$ is μ. The parameters of the log-logistic distribution are then $scale = \alpha = e^{\mu}$ and $shape = \frac{1}{\varphi} = \frac{1}{s}$. The expected value of the logistic distribution, μ, was then replaced by $ln(\beta_0 + \beta_1 SOIS)$ and related to the log-logistic distribution function so that there is a linear relationship between costs and SOIS with the expected cost being:

$$E(Cost) = (\beta_0 + \beta_1 SOIS)\frac{\varphi\pi}{sin(\varphi\pi)} \qquad (2)$$

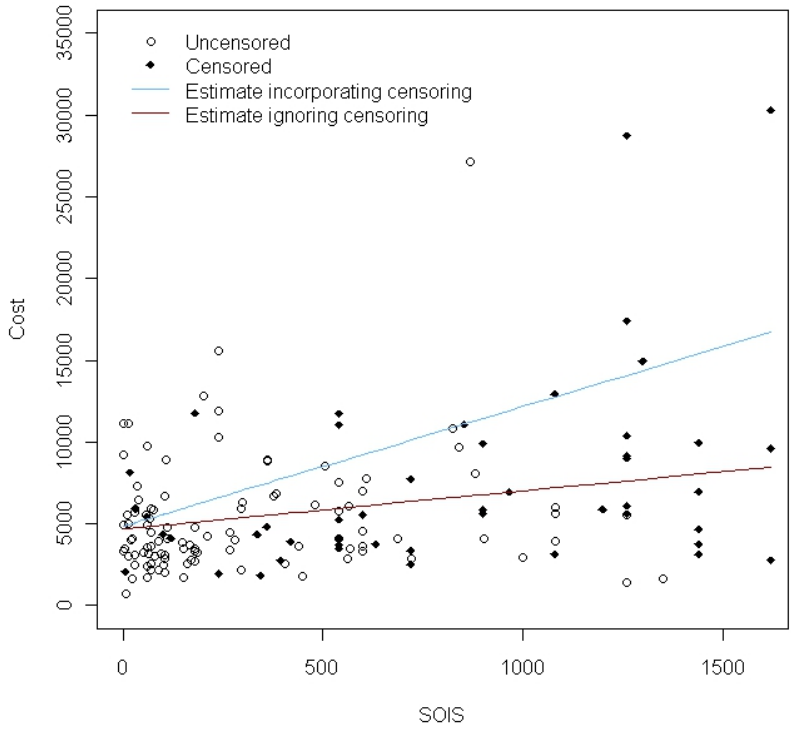
Right-censoring was taken into account as described before. The fitted values for these parameters are shown in Table 21. The relationship between cost and SOIS for patients who would or would not have been included in the Oxman et al[27] trial, and for patients with or without PHN is very similar to the relationship between cost and SOIS for an average HZ patient (results not shown).

Table 21: Parameter estimates for total direct medical cost of hospitalised HZ patients, as a function of SOIS

Parameter	Estimate	Standard error
β_0	3766.1929772	358.9905
β_1	5.7233071	1.168336
φ	0.3793714	0.03075893

The fitted curve taking right-censoring of the data into account (Figure 23) is used as input for our CUA.

Figure 23: Data and estimated direct medical costs for hospitalised HZ patients as a function of SOIS, without and with taking into account right-censoring of the data.



The personal direct costs for transport, not reimbursed care products and medication are presented in Table 22. Twelve of the patients had paid help at their house of which the costs were €231 (median), €704.6 (mean), €1 (minimum) and €2576 (maximum).

Table 22: Total direct personal costs of a person hospitalised for HZ: number and percentage of respondents that indicated the different cost categories.

	Transport		Care products		Medication	
Cost	nr	perc	nr	perc	nr	perc
Less than €20	46	30.06%	73	47.71%	59	38.56%
Between €20 and €50	45	29.41%	14	9.15%	29	18.95%
More than €50	58	37.91%	23	15.03%	31	20.26%
Did not respond	4	2.61%	47	30.72%	34	22.22%

Only the not reimbursed care products and medication are considered here. nr=number of respondents, perc=percentage of respondents

Work loss for to a person hospitalised for HZ was estimated similarly as described for CP. 22 out of the 153 respondents could not go to work because of having HZ. These 22 respondents missed work for about 15 days (median), the mean is 25.3 days, and the maximum 128 days. The median cost related to work loss for the complete sample is €0, the mean €599.9 and the maximum €22,790. Fourteen respondents indicated that somebody else could not go to work because them having HZ. These other persons missed work for about 2 days (median), the mean is 3 days, and the maximum 10 days. The median cost related to work loss for someone else than the person having HZ for the complete sample is €0, the mean €47.34 and the maximum €1781.

2.3.2 Cost for ambulatory care related to CP and HZ

2.3.2.1 Costs for ambulatory care related to CP

Sixty-six of the 70 responses (94.29%) were completed by the parent of the child that had CP and one response was from an adult who experienced CP herself. 91.38% of the children with varicella were below 4 years of age, the adult was 28 years, and no age was available for 11 of the respondents. The highest level of education was 'hogeschool/école supérieure' or university for 91.43% of the respondents with the remaining respondents being equally distributed between technical education and general secondary education. Thirty-nine (55.71%) of the respondents indicated that the patients had scars from varicella.

As this NCSF survey was done using an open call (see before), we are not sure on the representativeness of the respondents for the Belgian population, i.e. there may be bias towards more severe CP cases. Comparison with the Child&Family survey on ambulatory CP patients however, does not indicate such a bias:

The NCSF survey is compared with the Child&Family survey in terms of physician consultations (Table 23), duration of disease (Table 24). The patient that went to hospital in the Child&Family survey was not included in this comparison. This patient went to the GP once, and was sick for 14 days and had pneumonia. In the NCSF respectively the Child&Family survey, 17.39% respectively 12.15% of patients had co-morbidities.

Table 23: Comparison of NCSF and Child&Family survey on ambulatory CP patients, with respect to physician consultations.

	NCSF survey	Child&Family survey
Patients that do not go to a doctor	42.86%	38.32%
Patients that go only to a GP	50%	43.93%
Patients that go to paediatrician	7.14%	17.76%

Table 24: Comparison of NCSF and Child&Family survey on ambulatory CP patients, with respect to the number of days sick.

	NCSF survey	Child&Family survey
Min	1	0
Q1	4	4
Median	6	7
Mean	7	7
Q3	9	10
Max	25	21
Standard deviation	5	4

The direct medical costs of patients in the NCSF survey are summarised in Table 25. Twenty-eight patients (40%) had zero costs and therefore the summary statistics are provided for the entire sample and after excluding patients with zero costs.

Table 25: Summary statistics of the total costs of ambulatory CP patients from the NCSF survey, including ('all costs') and excluding patients with zero costs.

	All costs			Excluding zero costs		
Summary statistics	**Co-payments**	**NHS**	**Total**	**Co-payments**	**NHS**	**Total**
Min	0	0	0	0.89	1.79	2.68
1st Quartile	0	0	0	5.14	18.44	22.50
Median	4.02	16.86	22.46	8.09	21.72	32.57
Mean	5.60	15.24	20.84	9.56	25.40	34.73
3rd Quartile	8.12	23.57	34.00	12.40	25.91	34.49
Max	36.04	74.30	98.20	36.040	74.30	98.20
Standard deviation	7.30	16.42	22.99	7.30	13.76	19.88

NHS: National Health care System

Patients that do not have any physician visits have a cost which is close to zero (Table 26) and therefore we assume a zero cost for such patients. The difference in costs between patients that visited a GP or paediatrician is rather small (Table 26), so we estimate a single cost for them (also to increase the sample size). No relationship between cost and duration of disease, and cost and age was found (results not shown), but costs are slightly higher for patients with co-morbidity compared to patients without co-morbidity (Table 27).

Table 26: Summary statistics of the total cost of ambulatory CP patients from the NCSF survey, according to whether they consulted a physician.

	Patients that did not consult any physician	Patients that consulted a GP	Patients that consulted a paediatrician
Number of patients (percentage)	30 (42.86%)	35 (50%)	5 (7.14%)
Min	€0	€18.61	€33.71
1st Quartile	€0	€22.50	€33.71
Median cost	€0	€30.82	€34.00
Mean cost	€0.62	€32.78	€58.50
3rd Quartile	€0	€34.34	€92.87
Max	€15.95	€92.68	€98.20
Standard deviation	€2.94	€14.64	€33.86

Table 27: Summary statistics of the total cost of ambulatory CP patients from the NCSF survey, according to whether they had co-morbidities.

Summary statistics	Patients without co-morbidity	Patients with co-morbidity
Min	0	0
1st Quartile	0	16.84
Median	20	25.23
Mean	19.25	28.22
3rd Quartile	34	34.46
Max	92.87	98.20
Standard deviation	22.32	26.57

A shifted log-logistic distribution fitted the cost of CP patients with any form of physician consultations best. The distribution was shifted with a value of €18, as the minimum cost for a physician visit is €18, not €0. The expected value of the costs is therefore estimated as follows with the fitted parameters shown in Table 28:

$$Cost = \alpha \frac{\varphi\pi}{sin(\varphi\pi)} + 18$$

Table 28: Parameter estimates for the cost of CP patients who consult a physician.

Parameter	Estimate	Standard deviation
α	11.6011168	1.817222
φ	0.5689891	0.07490206

The personal direct costs for transport, not reimbursed care products and medication are presented in Table 29. Eight respondents (11.43%) had paid help at home, the costs related to this ranged from €6 to €224. Twenty-nine respondents (41.43%) had work loss with a median duration of 2 days (mean = 2.241, maximum = 8). The cost related to work loss among all respondents is €0 (median) (mean = €161.80, maximum = €1424.54).

Table 29: Total direct personal costs of ambulatory CP patients: number and percentage of respondents that indicated the different cost categories.

	Transport		Care products		Medication	
Cost	nr	perc	nr	perc	nr	perc
Less than €20	44	62.86%	59	84.29%	51	72.86%
Between €20 and €50	0	0%	5	7.14%	3	4.29%
More than €50	0	0%	0	0%	0	0%
Did not respond	26	37.14%	6	8.57%	16	22.86%

2.3.2.2 Costs for ambulatory care related to HZ

140 patients completed the NCSF questionnaire, but 9 of them were removed as they were hospitalised for HZ, and with this sample we want to estimate costs for patients not being hospitalised for HZ.

The majority of the questionnaires were completed by the person that had HZ (94%), the remaining questionnaires were completed by the partner or the child of the person with HZ, or by someone else. For 33% of the respondents the highest level of education was higher education ('hogeschool/école supérieure' or university), for 18% of the respondents general secondary education and for another 18% of the respondents secondary vocational education. Patients were sick on average for 110.9 days (mean=110.9, median=33.5, range=0-2159). However, 32% of these patients were still sick because of HZ at the moment they completed the questionnaire, for 78% of

the patients it was the first time they had HZ. 40% of the patients reported they suffered from another disease during their HZ episode. A clinician went through the responses of the survey to asses if the patients would have been excluded from the Oxman et al[27] trial based on the conditions of the immune system (Table 30). 98.5% of the patients that would not have been excluded, visited at least once a GP.

Table 30: Ambulatory HZ patients included in the NCSF survey by age group, patients that would have been excluded from the Oxman et al[27] trial based on the conditions of the immune system ('excluded'), all patients, and the proportion of excluded patients from all patients.

Age	Excluded	All	excluded/all
<60	23	44	52%
60-69	12	42	29%
70-79	12	36	33%
80 and older	3	8	38%
ages 60 and older	27	86	31%
all ages	50	130	38%

Table 31 presents the pain the persons with HZ experienced, based on a pain scale from 1 (no pain) to 10 (worst pain imaginable).

Table 31: Pain experienced by non-hospitalised HZ patients. Worst, least and average pain during their entire HZ period on a scale from 1 (no pain) to 10 (worst pain imaginable).

Pain score	Worst pain		Least pain		Average pain	
	nr	perc	nr	perc	nr	perc
0	1	0.77%	14	10.69%	1	0.76%
1	2	1.54%	23	17.56%	4	3.05%
2	4	3.08%	24	18.32%	18	13.74%
3	8	6.15%	25	19.08%	13	9.92%
4	5	3.85%	13	9.92%	13	9.92%
5	7	5.39%	10	7.63%	29	22.14%
6	8	6.15%	6	4.58%	24	18.32%
7	15	11.54%	10	7.63%	14	10.69%
8	32	24.62%	3	2.29%	10	7.63%
9	16	12.31%	0	0%	3	2.29%
10	32	24.62%	3	2.29%	2	1.53%

nr=number of respondents, perc=percentage of respondents

The direct medical costs are presented in Table 32. There is a positive relationship between the numbers of day sick and the total direct medical costs (results not shown).

Table 32: Summary of costs paid by the National Health care System ('NHS'), co-payments ('other') and total cost ('total') for direct medical costs for an ambulatory HZ patient.

Summary statistic	Other (€)	NHS (€)	Total (€)
Min	0	0	0
1st Quartile	8.12	33.42	44.92
Median	18.93	81.16	101.50
Mean	60.44	186.40	246.80
3rd Quartile	69.97	220.90	290.20
Max	1255.0	1640.00	2148.00
Standard deviation	130.14	261.84	348.66

Using @Risk, we estimate that the direct medical cost of an ambulatory HZ patient follows a log-logistic distribution.

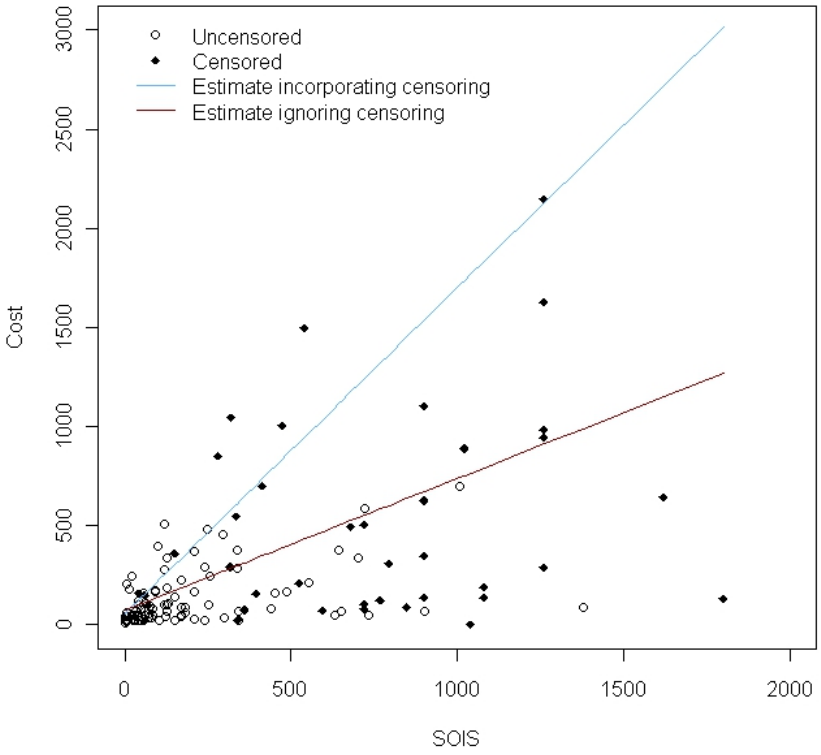
For the same reason as described for hospitalised HZ patients, we estimate direct medical cost for an ambulatory HZ patient as a function of SOIS. A second reason is that it allows to correct for the possible bias towards more severe HZ cases in the NCSF survey in ambulatory HZ patients. Indeed, the average (median) SOIS of the HZ ambulatory patients from the NCSF study are quite high (354.9 (168.0)) in comparison with the ones obtained by Scott et al[34] and Drolet et al[46] (Table 10), especially when knowing that the NCSF study includes *all* ages and only includes ambulatory treated patients. As a bias towards more severe HZ cases may lead to an overestimation of the average cost for a HZ patient, a correction according to HZ disease severity seems highly appropriate. This can be done by plugging the estimate of severity (SOIS) of an average ambulatory HZ case from above (based on the Scott et al study[34] or the Drolet et al study[46]) into a model of cost by SOIS. As such, we get the cost for an average ambulatory HZ case in Belgium.

Hence, we fitted models to estimate cost of an ambulatory HZ patient as a function of SOIS. Two models are similar in terms of goodness-of-fit, but describe the relationship between cost and SOIS quite differently. One model describes cost of an ambulatory HZ patients to increase linearly with SOIS ('linear model'), the other model describes cost as a power function of SOIS ('power model'). The linear model is the same as described for hospitalised HZ patients (Equation 1). Its parameter estimates (taking into account the right-censoring of the data) are shown in Table 33, the fitted curves in Figure 24.

Table 33: Parameter estimates for the cost of ambulatory HZ patients with a linear relationship between cost and SOIS

Parameter	Estimate	Standard error of estimate
β_0	26.1498949	7.217179
β_1	0.7595802	0.1241694
φ	0.6314680	0.05490805

Figure 24: Data and estimated direct medical costs for ambulatory HZ patients as a function of SOIS, without and with taking into account right-censoring of the data.



The power model is the following:

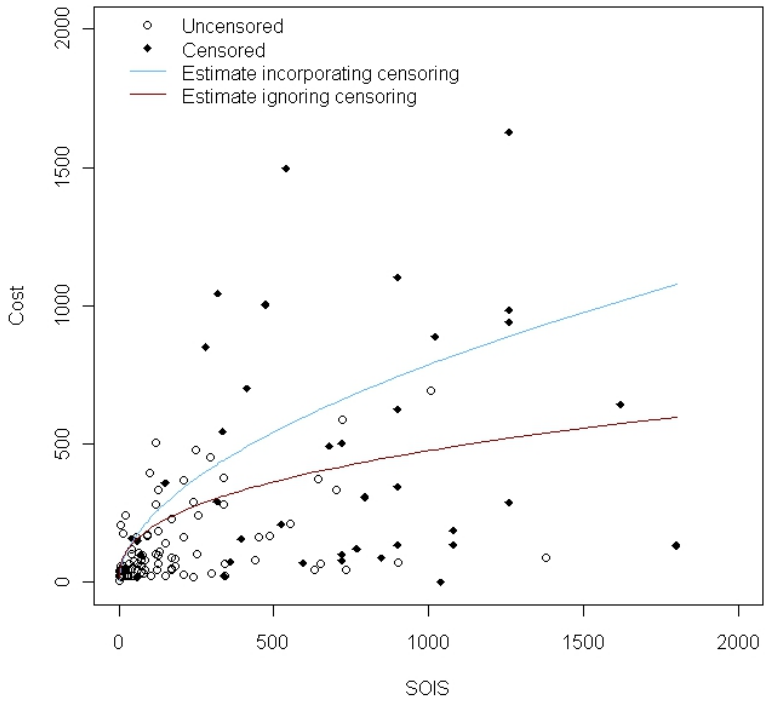
$$E[Cost] = e^{(\beta_0+\beta_1 \log(SOIS+0.1))} \frac{\varphi\pi}{sin(\varphi\pi)}$$

Its parameter estimates (taking into account the right-censoring of the data) are shown in Table 34, the fitted curves in Figure 25.

Table 34: Parameter estimates for the cost of ambulatory HZ patients with the relationship between cost and SOIS being a power function.

Parameter	Estimate	Standard error of estimate
β_0	2.0546814	0.2801144
β_1	0.5343038	0.05794554
φ	0.6785302	0.05838307

Figure 25: Estimated model for ambulatory HZ costs with a logarithmic relationship between costs and SOIS.



As the power model is slightly better than the linear model in terms of goodness-of-fit (squared error=88466 (power model) versus 98900 (linear model)), this model is used as input in CUA. However, the impact on the results of the CUA of using the linear model instead of the power model is explored. The relationship between cost and SOIS is for patients who would or would not have been included in the Oxman et al[27] trial, and for patients with or without PHN is very similar to the relationship between cost and SOIS for an average HZ patient (results not shown).

The personal direct costs for transport, not reimbursed care products and medication are presented in Table 12. Seven of the patients had paid help at their house of which the costs were €14 (median), €80.67 (mean), €1 (minimum) and €414.72 (maximum).

Table 12 : Total direct personal costs of an ambulatory HZ patient: number and percentage of respondents that indicated the different cost categories.

	Transport		Care products		Medication	
Cost	nr	perc	nr	perc	nr	perc
Less than €20	90	68.70%	67	51.15%	29	22.14%
Between €20 and €50	18	13.74%	18	13.74%	38	29.01%
More than €50	9	6.87%	17	12.98%	57	43.51%
Did not respond	14	10.69%	29	22.14%	7	5.34%

Only the not reimbursed care products and medication are considered here. nr=number of respondents, perc=percentage of respondents

Work loss for an ambulatory HZ patient was estimated similarly as described for CP hospitalised persons. 25 out of the 131 respondents could not go to work because of having HZ. These 25 respondents missed work for about eight days (median), the mean is 9.87 days, and the maximum 39 days. The median cost related to work loss for the complete sample is €0, the mean €233.8 and the maximum €4,452. One respondent indicated that somebody else could not go to work because of him/her having HZ, and that this person missed work for one day.

2.4 CP AND HZ RELATED LOSS IN QOL

2.4.1 CP related loss in QoL

The quality of life lost due to CP is estimated with the Child & Family survey through the EQ5D questionnaire. Twenty-eight (25.93%) of the respondents did not fill in at least one of the EQ5D questions likely because these questions were believed irrelevant for young children (e.g. one of the questions asks if the child had problems caring for him/herself). Therefore unanswered questions were treated as if the child had no impairment on their quality of life except if any comments were written indicating otherwise. This was the case for one respondent, who indicated that his/her child had fever and low energy levels. The quality adjusted life weeks lost for a patient is calculated as one minus the EQ5D score multiplied by the number of weeks sick.

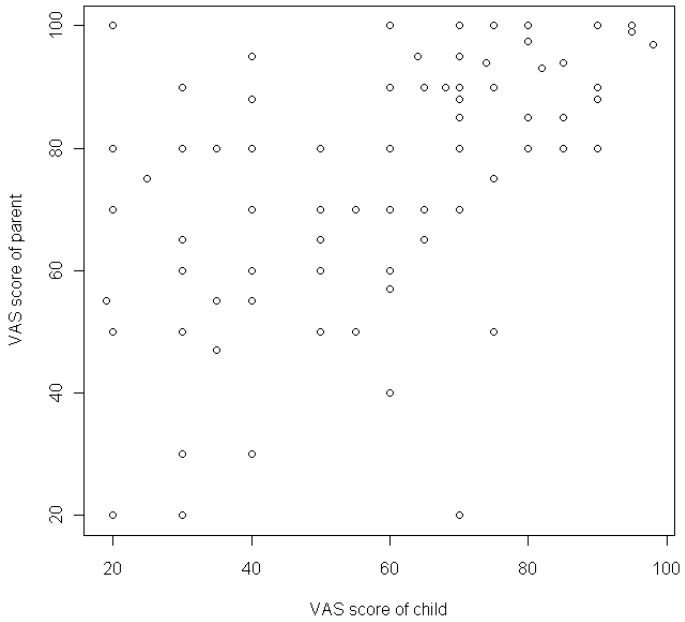
The average quality adjusted life weeks lost due to CP disease in the Child & Family survey is 0.42 (median=0.04, min=0, max=2.76), does not depend on age, but is higher for patients who consult a physician compared to patients not consulting a physician (Table 34).

Table 34: Summary statistics for the quality adjusted life weeks lost due to CP disease (data from the Child & Family survey).

	Patients not consulting a physician	Patients consulting a GP but not a paediatrician	Patients consulting a paediatrician (includes 4 patients that also consulted a GP)
Number of patients	41	48	19
Min	0	0	0
Q1	0	0.1523	0.09193
Median	0.1468	0.3249	0.30690
Mean	0.2183	0.5862	0.43180
Q3	0.3057	0.7670	0.65200
Max	1.0190	2.7600	1.82400
Standard deviation	0.2601200	0.6624332	0.4662475

Respondents also had to indicate the health state of their child and themselves at the worst time of the disease using a visual analogue scale (VAS). This VAS score is a number between 0 and 100, with 100 indicating the best possible health and 0 the worst possible health one can have. The VAS scores of the parents and their children are presented in Figure 26.

Figure 26: VAS scores of children and parents of children with CP (data NCSF survey)



An exponential distribution fitted the quality adjusted life weeks lost best. The expected value of an exponential distribution is $1/rate$, and is modelled to depend on whether patients consult a physician yes or no ('$PhysInd$', 1=yes, 2=no), i.e. $\frac{1}{rate} = \beta_0 + \beta_1 PhysInd$. The fitted parameters are shown in Table 36, and are almost the same when including or excluding the one patient that was hospitalised (the quality adjusted life weeks lost for this patient is 0.896).

Table 36: Estimated parameters for the quality adjusted life weeks lost due to CP disease (data Child&Family survey).

Parameter	Fitted value	Standard deviation of fitted value
β_0	0.2183061	0.03451433
β_1	0.3251415	0.07572962

On average a child with CP has quality of adjusted life years lost of 0.010 (if consulting a physician) or 0.004 (when no physician is consulted). The quality of adjusted life years for the hospitalised child is 0.017. Note that the Child&Family survey only includes children below three years of age. However, we know of no studies that measure loss in QoL due to CP directly in adults. Some studies derived it indirectly: Smith and Roberts[48] derived QoL due to CP from a study of utility values for other medical conditions[49]. Merrett et al[50] estimated QALY loss for newly arrived immigrants and refugees in Canada, to be 0.006, 0.009 or 0.012 for a varicella case without complication, hospitalized for supportive care and hospitalized for complications respectively (based on Brisson and Edmunds[51] and Smith and Roberts[48]). The latter QALY loss estimates for adults are quite low compared to what we measured for children in Belgium. For our analysis, we assume QALY loss according to different types of medical care utilisation (hospitalisation, ambulatory care, no medical care), to be independent of age. Note however that the average QALY loss for an adult person (older than 12) with CP will be higher than the average QALY loss for a child with CP, as adults with CP are more likely to seek medical care (see above). Also, we investigate the impact of taken into account QALY loss for one caregiver of a person with CP. For this, we assume such a caregiver has the same QALY loss as when having a child with rotavirus disease[52].

2.4.2 HZ related loss in QoL

HZ patients can suffer from (the pain related to) their illness for a long time period (up to several years). This makes it very difficult and time-consuming to measure loss in QoL for the complete HZ period, limiting the scope to include this aspect in the surveys of the current report. However, several previous studies followed HZ patients for a relatively long time (6 months or more) to measure their pain and loss in QoL. Many of them focused only on patients with PHN (post-herpetic neuralgia, often defined as pain lasting longer than 3 months[53-56]. Others were part of clinical trials and used very strict inclusion criteria which not necessarily reflect the general population (e.g. Opstelten et al[57], and Bala et al[58] measured loss in QoL only in patients aged 65-70). We know of only a few prospective observational studies that measure pain due to HZ in the general community[7, 34, 36, 59, 60]. It is however difficult to compare their results as pain was measured differently, and the population considered was different (with respect to age distribution and the inclusion/exclusion of immonocompromised people). Also, only the Scott et al[34] and the Drolet et al[7, 47] studies measured loss in QoL due to HZ. As Drolet et al[47] only present EQ-5D scores of the patients at recruitment and three other fixed points in time, and not for the entire HZ episode, we will use the Scott et al[34] data to quantify average loss in QoL for an average HZ patient seeking medical care (we had access to the raw data from this study).

We will estimate average loss in QoL by SOIS (rather than directly by age), because, similarly as for costs, this allows us to look at the impact of the vaccine on HZ related loss in QoL when considering its efficacy against BOI.

The data from Scott et al[34] contained an utility score measured at baseline, and four weeks, three months and six months from study initiation. The total number of quality adjusted life weeks (QALWs) lived by each patient was estimated by constructing a line between the observed utility values and integrating the area under the curve. The maximum value of this area in a six month period is 26 weeks and so the difference between the area under the utility curve and 26 was the number of QALWs lost by each patient due to HZ. The utility value for some patients were less than one by the end of six months indicating that the patient was still experiencing some discomfort due to HZ at the end of the study. The total number of QALWs lost for such a patient is therefore right-censored. As previously described, some patients in the Scott et al[34] database were lost to follow up or died during the study and therefore their QALWs lost were also right censored.

The exponential distribution fitted best the QALWs lost (based on uncensored data only). The expected value of this exponential distribution was then modelled as a function of SOIS. Data exploration indicated that a power function with an intercept provided a satisfactory description of the relationship between QALWs lost and SOIS:

$$E(QALWs\ lost) = \beta_0 + \beta_1 SOIS^{\beta_2}$$

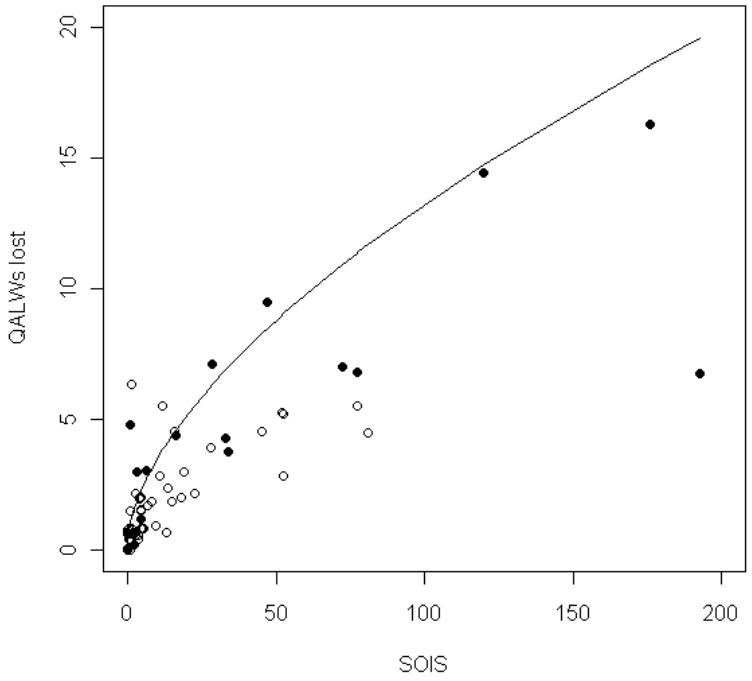
The parameters were estimated by correcting for the right-censoring as described before (Table 37).

Table 37: Parameter estimates for Qality of Life Weeks lost related to HZ, as a function of SOIS.

Variable	Estimated value	Estimated standard error
β_0	0.2712	0.2247
β_1	0.7899	0.3335
β_2	0.6076	0.1378

The data and the fitted curve between QALWs lost and SOIS is shown Figure 27. This relationship is similar for immunocompetent persons. The fitted curve (i.e. the estimated parameters of the curves) is used as input for our CUA.

Figure 27: Relationship between QALWs and SOIS: Scott et al data (circles) and fitted curve (solid line).

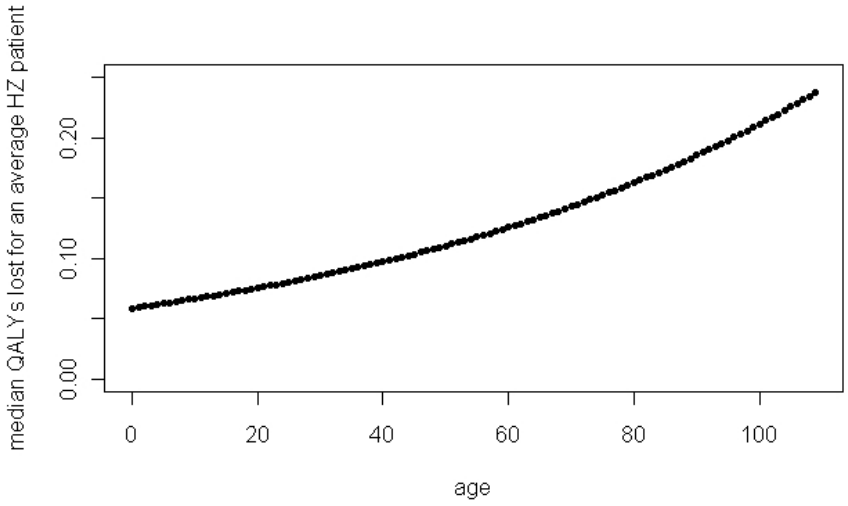


Open circles represent uncensored cases and closed circles are right-censored.

When plugging the SOIS's by age (estimated before, see p.29) in the function just described, we get the QALY's lost for an average HZ case by age (see Figure 28).

Note that with our approach we likely overestimation the QALY loss due to HZ, especially for the older age groups. This is because we assume that people without HZ have utility scores of 1. From Kind et al (1998), who measured health of a representative sample of the population of the United Kingdom by using the EuroQoL EQ-5D questionnaire, we can read that utility score (non disease specific) decreases with increasing age. This will be further discussed in the Discussion section of this report.

Figure 28: Median estimated QALY's lost for an average HZ patient, by age (Scott et al 2006 data).



2.5 BURDEN OF BREAKTHROUGH CP

Approximately one in every five children who receives one dose of varicella vaccine may develop CP, also known as breakthrough disease, if exposed to varicella-zoster virus. Chaves et al[61] show that this breakthrough disease in vaccinated children 1–14 years of age, was most often mild and modified. The symptoms and health care use that possibly impact on average cost and QALY loss, such as duration of fever and rash, complications and medication, all occur about 50% less in vaccinated persons, compared to unvaccinated persons[61]. Therefore, we assume average cost and average QALY loss for a breakthrough CP case to be half that of a primary CP case. However, Chaves et al[61] also found that vaccinated persons visited almost 3 times more often a health care provider (not further specified) than unvaccinated persons. The authors relate this to an atypical disease presentation diagnostic which challenges the health care provider. Therefore we will explore how sensitive the cost-effectiveness of scenario's considering only a single dose of varicella vaccination are to different values for the cost and QALY loss of breakthrough CP cases compared to primary CP cases.

2.6 HZ IN IMMUNOCOMPETENT POPULATION

We run an analysis assuming only HZ episodes in immuncompetent persons can be avoided by introducing a vaccination program. This is because the Zostavax® vaccine is tested in, and recommended for immunocompetent persons only. However, only considering the immunocompetent population may underestimate the potential benefit of the vaccine. For instance in practice, immunocompromised people are sometimes vaccinated, as the risk of vaccination is regarded smaller than the risk for HZ. Also, people may be vaccinated before they become immunocompromised. In that case it is however not clear if the protection of the vaccine when the person becomes immunocompromised, is comparable to the protection in immunocompetent persons. Although (some groups of) immunocompromised persons may also benefit from Zostavax® vaccination, at the moment of this writing, no trials on safety and immunogenicity of zoster vaccine in such groups were completed. Oxman[62] however wrote such a trial is underway in HIV-1–infected patients who are receiving antiretroviral therapy. A scenario assuming only HZ episodes in immunocompetent people can be avoided by vaccination provides a lower estimate, i.e. the minimum number of people that can benefit from vaccination. On the other hand, assuming that everybody can be vaccinated serves as an upper limit, i.e. the maximum number of people that can benefit from vaccination.

Belgian data on the proportion of HZ patients being immunocompromised by age are presented in Table 17 and Table 30. Insinga et al[63] assessed HZ incidence based on the Medstat MarketScan database, containing health insurance enrolment and claims data from over 4 million U.S. individuals. Incidence was obtained for everybody, as well as for patients with evidence of recent care for transplantation, HIV infection or cancer. The latter groups of patients comprised 4.3%, respectively 11.7% of all HZ patients (age <50, respectively age>49). Pellissier et al[64] present data for finer age groups, referring to the same study (Table 35). Note that 'immunocompetent' is defined here as patients without evidence of recent care for transplantation, HIV infection or cancer.

Table 35: Data as presented in Pellissier et al[64] (except for last column).

Age	Immunocompetent	All	(1- immunocompetent)/all
60-69	6.94 [6.60;7.30]	5.90 [5.56;6.26]	15%
70-79	9.46 [9.00;9.90]	7.76 [7.20;8.10]	18%
80 and older	10.94 [10.30;11.60]	9.76 [9.02;10.32]	11%

Comparison of the two data sources (NCSF surveys and Pellissier et al/Insinga et al[63]) indicates that the proportion of HZ cases that are immunocompromised depends on the definition for 'immunocompromised'. Pellissier et al[64]/Insinga et al[63] may have underestimated the proportion of HZ patients that would have been excluded in the Oxman et al[27] trial, as they only used a selection of the exclusion criteria defined by Oxman et al[27]. Also, they only assessed 'immunocompromised status' on the moment of the person having HZ. Although the sample size of the NCSF survey is quite small, our selection based on the NCSF survey may be most accurate, as it was manually done by a clinician, based on the complete exclusion criteria list of Oxman et al[27], and based on several questions on having concomitant diseases at the moment of having HZ, as well as during the year preceding the moment of participation in the survey. As mentioned before, the respondents of the ambulatory NCSF survey may be biased towards more severe cases, and consequently may be biased towards a higher percentage of immunocompromised persons. Therefore, the scenario with only including immunocompetent persons serves as a lower limit, i.e. the minimum number of people that can benefit from Zostavax® vaccination.

Hence, for the scenario analysis only considering vaccine protection against HZ in immunocompetent persons (according to Oxman et al[27] inclusion criteria), the number of HZ hospitalisations and ambulatory cases estimated for Belgium, will be decreased by the (age-specific) proportions from Table 17 and Table 30. As the proportion of HZ hospitalizations in immunocompetent persons is lower than the proportion of HZ ambulatory patients that are immunocompetent, the proportion of HZ patients being hospitalized decreases when only taking into account patients complying with the Oxman et al[27] inclusion criteria.

No data are available on the proportion of the Belgian population that is immunocompetent. By doing analyses for different values of the coverage rate of vaccination, we explore the combined effect of the percentage of the Belgian population that is immunocompetent, and the percentage of them that are reached for Zostavax® vaccination. Also, it is likely that the lifeyears expected in the total population differs from that of the immunocompetent population, but because of lack of data on this, we assume no difference.

As it is unclear if the HZ related deaths registered in Belgium occurred in immunocompromised people, again, we choose the most conservative approach assuming no death in immunocompetent persons with HZ.

Estimated relationships between SOIS and age, cost and SOIS and QALY's lost and SOIS for immuncompetent HZ patients are described before. Note that based on the Scott et al[34] data, the average SOIS for an immunocompetent HZ case is slightly lower than for an average HZ case. This is the inverse of what was found from the NSCF surveys: for both hospitalized and ambulatory HZ patients, the average SOIS increases when immunocompromised patients are excluded (according to Oxman et al[27] criteria). Note however that what is considered to be 'immunocompetent' differs between the two data sources. Because of the absence of strong evidence pointing in a certain direction, and because the scenario considering only the immunocompetent population serves as a minimum (minimum number of persons that can benefit from the vaccine), we will use the Scott et al[34] data as it is the most conservative approach.

2.7 USE OF ANTIVIRAL MEDICATION FORHZ

In the Oxman et al SPS study[27] and the Drolet et al study[46] almost 90% of the people with HZ received antiviral medication. In the Scott et al study[34], 79% of the people over 50 years of age with HZ received antiviral medication. Preliminary data from the SIPH, show that in Belgium 70% of HZ cases who visited a GP for the first time for HZ, are treated with antiviral medication (n=306). For our analysis, this can have the following implications:

- If there is a synergetic effect of the vaccine and the use of antiviral medication, the efficacy of the vaccine for the Belgium population will be overestimated, as we use vaccine efficacy estimates based on the SPS study.
- Li et al[65] found some evidence that antiviral medication (oral acyclovir) reduces incidence of pain four weeks after the onset of rash. However, no evidence for a reduction in PHN incidence at 4 and 6 months after rash onset was found, and insufficient evidence was found for the effect of other antiviral treatments. If indeed antiviral medication decreases the duration and/or severity of HZ (i.e. the severity-of-illness score (SOIS)), the HZ related burden of illness in Belgium will be underestimated, as we use for this data on SOIS from Drolet et al[46] and Scott et al[34].

As we do not have information on a possible synergetic effect of the vaccine and the use of antiviral medication, and as we do not have sufficient detailed information on the influence of antiviral medication on the SOIS, these possible effects will not be quantified in our CUA.

2.8 VACCINE RELATED CHARACTERISTICS

2.8.1 Childhood VZV vaccination("chickenpox" vaccination)

2.8.1.1 Vaccine effectiveness

We adopt van Hoek et al[66]'s estimates of vaccine take and waning in our analyses of VZV vaccination strategies in childhood. Estimation was based on clinical trial data as presented by Brisson et al[67]. The values for take and waning are based on a clinical trial with an average of 2900-9000 plaque forming units. The rate of primary CP vaccine failure (p) observed in clinical trials has ranged from 0-6%[68-70], for the model p was set to 4% (cfr. Brisson et al[71]). The take for the vaccination responders was estimated to be 1 at base case, with a waning rate of 4.4% and 1.3% after 1 and 2 doses respectively (see Table 43). In sensitivity analysis, take of first dose is varied between 0.9936 and 0.932346, take of second dose between 0.999671 and 0.98621, waning rate after first dose between 1.5% and 6.7%, and waning rate after second dose between 0.5% and 2.6% (see Table 43).

2.8.1.2 Intervention costs and CP vaccine uptake

The marginal intervention costs consist of the purchasing costs as well as the marginal administration costs of the vaccine. All scenario's are run with the price of €43.46/dose, i.e. a reduction of 10% of the current retail price of Varilrix (the cheapest of the 2 vaccines), 10% as the minimal expected reduction due to bulk purchase of the vaccine in case of a public program .

Since the current infant immunization schedule should easily accommodate the additional vaccine, there is likely only a cost for the additional time vaccinators will need to take to explain and give the vaccine. This cost is assumed to be €5.

Assumed coverage of CP vaccination for the different vaccination scenario's:

- Coverage of 95% for vaccination at age 1 (based on coverage of measles vaccination in Flanders, Brussels and Wallonia[72, 73])
- Coverage of 90% for vaccination at age 4 and age 6 (based on coverage of polio vaccination in Flanders at age 6[73])
- Coverage of 80% for vaccination at age 11 (based on coverage of measles vaccination in Flanders, Brussels and Wallonia between age 10 and 12[73, 74])

2.8.2 Adult VZV booster vaccination("herpes zoster" vaccination)

Note that vaccination with the Zostavax® vaccine differs from classical vaccination because it is used to boost the cell-mediated immunity to VZV, rather than elicit this immunity.

2.8.2.1 Vaccine effectiveness

Literature

MORBIDITY

See Table 36 for an overview.

Table 36: Overview of existing data on HZ vaccine efficacy against burden-of-illness ('VEBOI'), HZ cases ('VEHZcases') and PHN ('VEPHN').

	VACCINE GROUP			PLACEBO GROUP			VACCINE EFFICACY		
VEBOI	over 3.2 years, Oxman et al NEJM 2005; Oxman et al JID 2008: no significant difference between age groups and gender								
	#confirmed cases	#subjects	**BOIscore**	#confirmed cases	#subjects	**BOIscore**	VE	Left 95%CI	Right 95%CI
all	315	19254	2.21	642	19247	5.68	**0.61**	0.51	0.69
age 60-69	122	10370	1.50	334	10356	4.33	**0.66**	0.52	0.76
age 70plus	193	8884	3.47	308	8891	7.78	**0.55**	0.40	0.67
male	181	11390	2.09	361	11337	5.81	**0.64**	0.51	0.73
female	134	7864	2.34	281	7910	5.47	**0.57**	0.40	0.70
VEHZcases	over 3.2 years, Oxman et al NEJM 2005 &FDA 2005; Oxman et al JID 2008: sign. difference between age groups; no info on gender found								
	#confirmed cases	#subjects	**personyears**	**#confirmed cases**	#subjects	**personyears**	VE		
all	315	19254	58203	642	19247	57736	**0.513**	0.442	0.576
age 60-69	122	10370	31323	334	10356	30953	**0.639**	0.555	0.709
age 70plus	193	8884	26881	308	8891	26783	**0.376**	0.25	0.481
VEPHN	over 4 years, Brisson et al 2007: efficacy in preventing PHN in subjects **with HZ**; only significant for age 70 and older								
	#PHN	**#Hzcases**		**#PHN**	**#Hzcases**				
age 70plus	18	191		56	304		**0.49**	*no CI's given*	*no CI's given*
age 70plus_modified	18	191		51	304		**0.44**	*no CI's given*	*no CI's given*
VEBOI by year after vaccination		FDA 2005							
Year after vac	#confirmed cases	#subjects	**BOIscore**	#confirmed cases	#subjects	**BOIscore**	VE	Left 95%CI	Right 95%CI
1	76	19254	0.427	201	19247	2.075	**0.794**	0.682	0.867
2	103	18994	0.801	194	18915	1.661	**0.518**	0.266	0.683
3	98	18626	0.809	171	18422	1.482	**0.454**	0.193	0.631
4	35	9942	0.367	70	9806	1.007	**0.635**	0.246	0.824
5	3	1906	0.094	6	1856	0.375	**0.748**	0.190	0.922
VEHZcases by year after vaccination			FDA 2005						
Year after vac	**#confirmed cases**	#subjects	**personyears**	**#confirmed cases**	#subjects	**personyears**	VE	Left 95%CI	Right 95%CI
1	76	19254	19132	201	19247	19081	**0.623**	0.507	0.714
2	103	18994	18827	194	18915	18679	**0.473**	0.328	0.589
3	98	18626	14505	171	18422	14327	**0.434**	0.270	0.563
4	35	9942	5412	70	9806	5325	**0.508**	0.252	0.682
5	3	1906	327	6	1856	324	**0.504**	-1.324	0.920
VEPHN by year after vaccination: Brisson et al 2007: VE in preventing PHN in subjects with HZ; age 70 and older; (only VEPHN over 4 yrs not modified was									
Year after vac	**#PHN**	**#Hzcases**		**#PHN**	**#Hzcases**				
1	4	43		23	105		**0.58**	*no CI's given*	*no CI's given*
2	6	66		14	85		**0.45**	*no CI's given*	*no CI's given*
3	6	60		13	80		**0.38**	*no CI's given*	*no CI's given*
4	2	22		6	34		**0.48**	*no CI's given*	*no CI's given*

Until now, the only study investigating the reduction in morbidity due to vaccination by means of Zostavax® is a randomized, double-blinded, placebo-controlled trial including 38546 subjects of the US (Oxman et al[27], Shingles Prevention Study (SPS)). Individuals included were 60 years or older (median age 69 with about 7% older than 79) and they received one dose of 0.5 ml CP vaccine (PFU between 18700-60000).

In total 957 subjects developed HZ during the trial and these subjects received standard treatment comprising famciclovir. The placebo group accounted for 11.12 cases per 1000 person-years whereas the vaccinated group had only 5.42 cases per 1000 person years. This significant difference was also numerated in the so-called vaccine efficacy (VE) defined as 1 – relative risk (= incidence in vaccinated group divided by the incidence in placebo group) and led to an overall efficacy of 51.3%. The VE < 70y was found to be significantly higher than the VE ≥ 70y (63.9% vs. 37.6%). No significant difference in VE between males and females was found. The mean duration of a HZ episode was significant reduced by vaccination (24 days vs. 21 days).The NNT to prevent one HZ case (during the observation period) was estimated by Fekete et al[75] at 59[50-72].

Post-herpetic neuralgia (PHN) occurred in 0.46cases per 1000 person years in the vaccinated group, compared to 1.38 cases per 1000 person years in the placebo group, leading to a vaccine efficacy of 66.5%. PHN was defined as the occurrence of pain related to HZ that was rated a score of 3 or more on a specific question of the Zoster Brief Pain Inventory[44] assessing the "worst pain (between 0 no pain and 10 pain as bad you can imagine) persisting or appearing 90 days or more after onset of symptoms". The results of vaccination were similar with different definitions concerning the time-interval of PHN. There was a tendency towards a greater absolute effect on PHN incidence for ages ≥ 70y not reflected by using VE as outcome variable. It is noteworthy to report the larger use of opioids within the placebo group. A similar calculation of the NNT for PHN was estimated by Fekete et al[75] to be 364 [259-577].

Primary endpoint was efficacy in reducing the herpes-zoster burden-of-illness-score (BOI).As mentioned before, BOI is a severity-by-duration measure of the total pain and discomfort associated with HZ. For each HZ case, a severity-of-illness score (SOIS) was obtained, defined as the area under the curve of herpes-zoster pain (answer to the 'worst pain' question in the Zoster Brief Pain Inventory), plotted against time during the 182-day period after the onset of rash. Hence, subjects could have SOIS ranging from 0 to 1820. The BOI represented the average SOIS among all subjects in the vaccine and placebo groups (with a SOIS of 0 for all subjects in whom HZ did not develop during the study period). This average was calculated as the sum of the SOIS's of all members of a group divided by the total number of subjects in the group (see also Chang et al[45]). VE_{BOI} was calculated as 1 – relative risk, with relative risk being the BOI in the vaccinated group divided by the BOI in the placebo group. Overall the VE_{BOI} was 61.1% and found not to be significantly different for age and gender, although there was a tendency towards a greater absolute effect when ≥ 70y and in males compared to females.

A subsequent analysis of the cost-effectiveness by Rothberg[76] reported no effect on incidence reduction of PHN beyond that achieved by the reduction of HZ in total. However, Brisson[77] commented that there existed a significant effect beyond that achieved by HZ reduction for the age group ≥ 70y.

SAFETY

There were no differences between the two groups concerning death and an adverse-event substudy (n = 6616) reported no differences in the incidence of hospitalization. This latter substudy reported however significant more adverse events (mainly injection site related such as erythema, pain, swelling and pruritus) and significant more serious adverse advents (1.9% vs. 1.3%) at day 42 after vaccination related to vaccination. This increase in serious adverse advents was however not noted in the overall study population.

In 2007 a randomized clinical trial (Tyring et al[78]) in subjects ≥ 50 years of a higher potency Zostavax® vaccine (207000 PFU/0.65ml, n = 459) and a lower potency Zostavax® vaccine (58000 PFU/0.65ml, n = 233) found comparable adverse events (AEs) between these groups concerning systemic clinical AEs and injection-site AEs besides pain, tenderness, soreness and swelling being more detected in the higher potency group. There were no deaths and no serious clinical events related to vaccination. 10 rashes were reported within 42 days postvaccination. "40% of subjects in each vaccine potency group reported a systemic clinical AE, whereas 60% of subjects reported one or more injection-site AEs".

A small (n = 21) study (Macaladad et al[79]) in non-European countries focusing on the effect of the antibody titer (negative, low-positive, high-positive) in ≥ 30 year old subjects after using a 50000 PFU vaccine found no vaccine-related serious AE and no confirmed CP or CP-like rash > 50 lesions. A study by Gilderman et al[80] in subjects ≥ 50 years between a Zostavax® frozen formulation and a Zostavax® refrigerated formulation showed no vaccine-related serious events reported and similar safety profiles (although clinical AE were more frequently reported for the frozen formulation, systemic clinical AEs were similar between groups).

A recently published article by the SPS group focusing on the safety of the Herpes Zoster Vaccine confirmed the earlier findings (Simberkoff et al, Annals of Internal Medicine, 2010). Within 42 days after inoculation vaccinated individuals showed significantly more local responses such as erythema, swelling and pruritus. A smaller substudy (N = 6575) showed a significantly higher incidence of serious adverse-events with some concerns about the cardiovascular events which, although absolutely higher for the vaccinated group (20 vs. 12), was found to be non-significant (P value 0.161, however 0.104 when examining only vascular pathology). The total study population showed a similar incidence of serious adverse events (P value 0.55 in case of vascular pathology). The authors conclude that perhaps due to non-randomization of the subgroups chance might have caused the difference between the vaccinated and the placebo group. For the entire study duration there were no differences between the two groups in terms of death and rates of hospitalization.

IMMUNOGENICITY

The immunogenicity was assessed at 2 substudies of SPS (Levin et al[81], Weinberg et al[82]). Both the cellular immune response (CMI) by means of IFN-gamma ELISPOT and Responder cell frequency (RCF) and humoral immunity by means of gpELISA were measured.

As compared to the baseline values the authors found at 6 weeks a RCF increase of ~ 50%, an ELISPOT increase of ~ 100% and a gpELISA increase of ~ 60% (rough estimate based on a graphical representation since numeric data were not given).

As compared to the placebo control group the authors found at 6 weeks a vaccine-induced boost of 85 % by RCF, 120% by ELISPOT and 78% by gpELISA. At 1 y they noted a boost of 42% by RCF, 60% by ELISPOT and 20% by gpELISA, therefore showing a decrease in all immune parameters from 6 weeks to 1 year. The VZV-CMI responses remained relatively constant over time, whereas the antibody responses declined 7%-15% per year after. After baseline, all responses of the vaccine recipients differed significantly from those of the placebo recipients.

For the placebo group it was noted that 1 week after HZ RCF and ELISPOT values were higher in subjects with lower HZ severity-of-illness scores and in those who did not develop PHN suggesting a reverse relationship between the cellular immune response at week 1 after onset of HZ and the morbidity caused by HZ. The VZV-immune responses at week 1 did not differ between vaccinated subjects with HZ and placebo recipients with HZ. At 3 weeks after rash onset there was no significant correlation between RCF/ELISPOT and morbidity. gpELISA titers were not correlated with morbidity at week 1, but showed a significant rise at week 3 for the subjects with higher morbidity (BOI/PHN). gpELISA titers, however, were higher for the placebo group at week 3, year 1 and year 3 after HZ onset compared to the titers for the vaccinated group.

This could mean that a lower morbidity for PHN when vaccinated could be correlated with lower antibody titers, and not as much with the cellular immune response.

The incidence of HZ after HZ is neglectable, therefore it is interesting to note that the CMI level one year and later after vaccination is comparable to the CMI level at the same time points after natural HZ. Only at 6 weeks the ELISPOT response of the natural HZ group was higher than the response of the vaccinated group. The gpELISA titer had the same characteristics at 6 weeks and had only a marginal difference afterwards.

The study by Gilderman et al[80] in subjects ≥ 50 years showed no difference in GMT-increase after 28 days between a Zostavax® frozen formulation and a Zostavax® refrigerated formulation.

Estimate HZ vaccine efficacy

Data on efficacy of the HZ vaccine is available for up to 5 years after vaccination (Zostavax® trial, Figure 29 and Figure 30), and no data exist for efficacy by year after vaccination, age at which the vaccine is given (60-69 or 70 and older) and gender together. However, the available data show that efficacy varies by these factors (although not always significantly, see Table 36). This is why we will use models to estimate the efficacy of HZ vaccine by year after vaccination (extending beyond 5 years after vaccination) and age to which people belong when vaccinated together. Different types of efficacies were measured in the Zostavax® trial: vaccine efficacy against Burden of Illness (VE_{BOI}, Figure 30), vaccine efficacy against the number of confirmed HZ cases ($VE_{hzcases}$, Figure 29), vaccine efficacy against the number of PHN cases[27]; and vaccine efficacy against PHN cases among HZ subjects (VE_{PHN})[77]. For our cost-utility analysis, in one scenario, $VE_{hzcases}$ is used, and in another scenario VE_{BOI} which incorporates duration and severity of disease. As PHN is defined in terms of duration (at least 3 months) and severity (pain of at least score 3) of HZ disease, estimates for efficacy in preventing PHN are not used, as such prevention is already incorporated in the estimates for VE_{BOI}. Note that VE_{BOI} only takes into account the duration and severity of HZ disease for the first 6 months after rash onset.

Moreover, a poster was presented at ICAAC/IDSA 2008, on Zostavax® vaccine efficacy up to 7 years after vaccination[83]. Data came from the same SPS trial as described in Oxman et al[27]. Values were presented for $VE_{HZcases}$ and VE_{BOI} by year after vaccination (up to 7 years, Figure 29 and Figure 30), but not by age. Values were also given for vaccine efficacy against the number of PHN cases in the total population, but not for vaccine efficacy against the number of PHN cases among HZ subjects (VE_{PHN}).

Figure 29: Zostavax® vaccine efficacy against number of HZ cases (VEhzcases) by year after vaccination: comparison of values from Oxman et al 2005 and ICAAC-IDSA poster 2008.

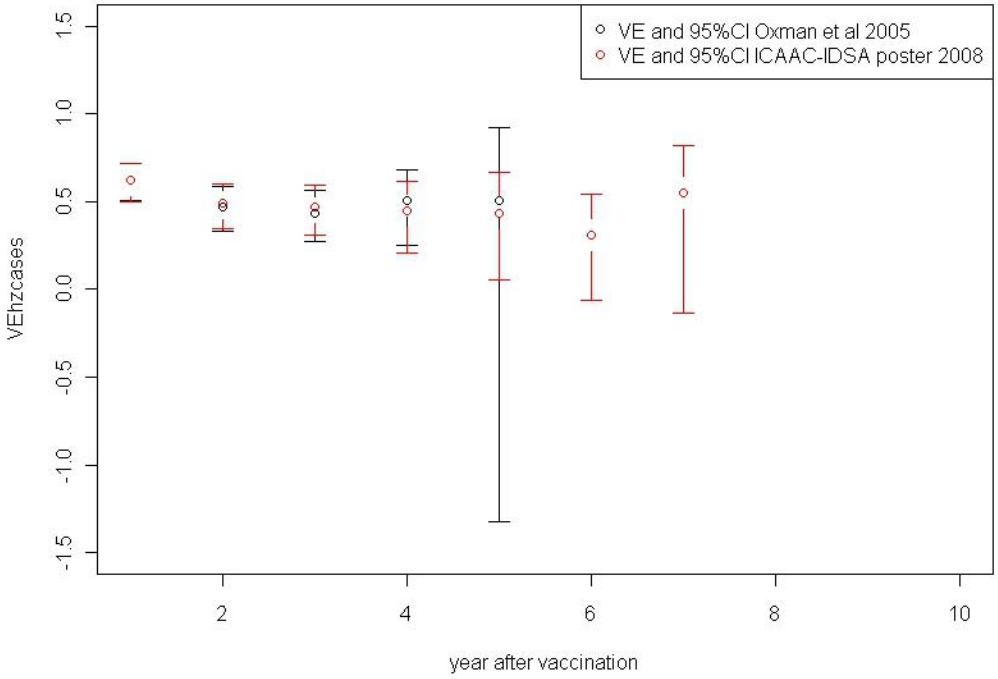
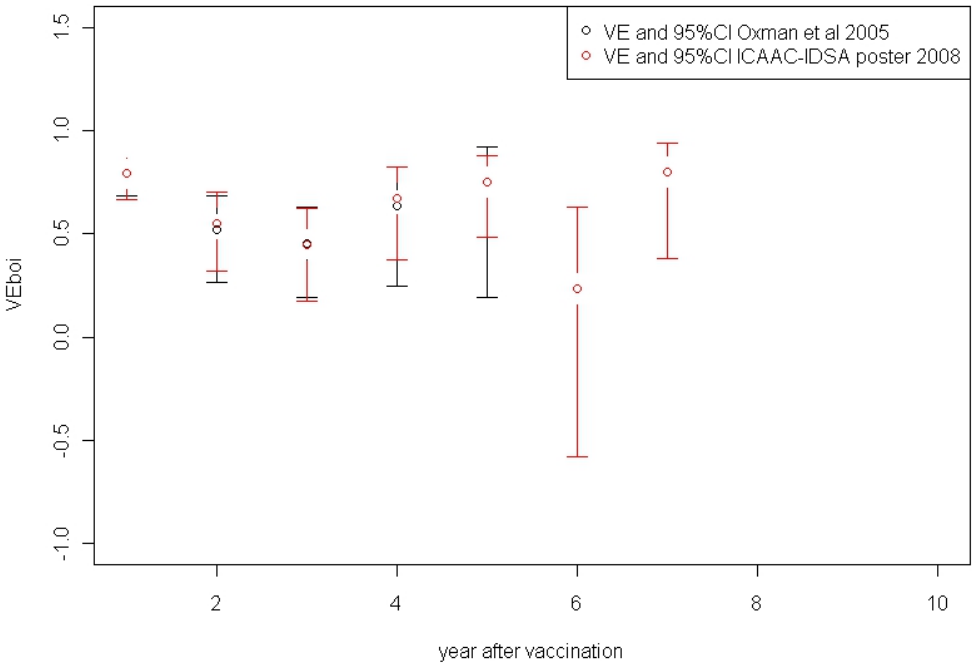


Figure 30: Zostavax® vaccine efficacy against HZ related BOI (VEboi) by year after vaccination: comparison of values from Oxman et al 2005 and ICAAC-IDSA poster 2008.



In summary following vaccine efficacy estimates will be obtained:

- $VE_{hzcases}$ by age and year after vaccination (based on the data for 5 years after vaccination and 7 years after vaccination separately)
- VE_{BOI} by year after vaccination

VE$_{HZcases}$ BY AGE AND YEAR AFTER VACCINATION

The next paragraphs describe (1) how VE$_{HZcases}$ is estimated by year after vaccination, (2) how VE$_{HZcases}$ is estimated by age, and (3) how step (1) and (2) are combined to obtain how VE$_{HZcases}$ changes by year after vaccination and age together.

1. VEhzcases by year after vaccination (step 1)

Estimates for VE$_{HZcases}$ are available for the first 5 years after vaccination. These could be used directly as input in the cost-effectiveness model, but then assumptions would have to be made for what happens after the 5th year. Also, efficacy after one year likely depends on efficacy for the previous year, which we would not take into account when we use the separate efficacy estimates for each year after vaccination. Therefore, we prefer to model how efficacy changes over time after vaccination.

The available data from the trial do not show a clear pattern of waning of efficacy. In the first 3 years after vaccination, efficacy tends to decrease, but in year 4 and 5 after vaccination, efficacy increases again, however, note that confidence intervals become also very large (Table 36). If we would try to model the data as accurately as possible (e.g. by using a generalized additive model with splines), we will get this initial decrease and thereafter increase in VE$_{hzcases}$. Extrapolating this over more years after vaccination will result in increasing efficacy, which is unlikely to happen in reality. More likely, efficacy will either stay constant over time or decrease, so this is what we assume for the models. (Note that this assumption would only be violated if boosting by wild-type virus is different between the vaccinated and placebo group). When fitting our models, we also take into account that we are less sure of the efficacy estimates 4 and 5 years after vaccination compared to the first years after vaccination.

The first model we fit: VE$_{hzcases}$ changes exponentially with time, based on 5 yrs

$$nrHZcases_{VACi} = [1 - \beta_1 e^{-\beta_2 years_i}] * \frac{nrHZcases_{PLi}}{personyears_{PLi}} * personyears_{VACi}$$

With:

- $nrHZcases_{VACi}$ denoting the annual number of HZ cases in the vaccinated group, obtained in the Zostavax® trial (see Table 39)
- $personyears_{VACi}$ denoting the total personyears of follow-up in the vaccinated group (see Table 39)
- $\frac{nrHZcases_{PLi}}{personyears_{PLi}}$ denoting the rate of HZ in the placebo group (see Table 39)
- $years_i$ denoting the years after vaccination (j=1,2,...,5)
- $[1 - \beta_1 e^{-\beta_2 years_i}]$ denoting the relative risk, or [1-vaccine efficacy VE$_{hzcases}$], with VE$_{hzcases}$ changing exponentially with years since vaccination, described by parameters β_1 and β_2.

So, instead of modelling VE$_{hzcases}$, the HZ incidence rate by year after vaccination is modelled directly. An advantage of modeling incidence rate rather than VE$_{hzcases}$, is that for the latter approach, we would have to make an assumption on the uncertainty distribution of VE, as only 95%CI's are available to us. In the model, the number of confirmed HZ cases is assumed to be Poisson distributed, and to change exponentially with time. By including personyears of follow-up as offset, we take into account that we have stronger evidence for the first years after vaccination compared to the later years. By including the rate of HZ in the placebo group ($\frac{\text{nrHZcases}_{PLi}}{\text{personyears}_{PLi}}$), we correct the rate of HZ in the vaccine group (and consequently the estimated vaccine efficacy), for the baseline rate of HZ. Parameters β_1 and β_2 are estimated using maximum likelihood.

Other possible models for VE$_{hzcases}$:

In total, 7 different models are fitted on the data, describing 7 different ways in how VE$_{hzcases}$ changes over time since vaccination (Table 37, for details see Bilcke et al[84]). The same models are also fitted on the data for 7 years after vaccination.

Comparing models:
Models are compared with the corrected Akaike Information Criterion (AICc)[85]. Fitted models are very comparable with respect to their AICc value: no single model is clearly better than any of the other models (Table 37). Models fitted on 7-year data estimate a slightly slower waning of efficacy compared to models fitted on 5-year data (Table 37).

Table 37: Functions for how vaccine efficacy against the number of herpes zoster cases (VE_i) changes with years since vaccination ($years_i$), maximum likelihood estimates of parameters and AICc values for models fitted on data for a period of 5 and 7 years after vaccination. (NA=not applicable)

		data 5 years [86]			data 7 years [83]		
Waning functions		$\beta_1 \pm$ SE	$\beta_2 \pm$ SE	AICc	$\beta_1 \pm$ SE	$\beta_2 \pm$ SE	AICc
power	$VE_i = e^{-\beta_1 years_i{}^{-\beta_2}}$	0.49±0.07	0.28+0.11	39.2	0.49±0.07	0.26±0.08	49.3
logarithmic	$VE_i = \beta_1 - \beta_2 \log(years_i)$	0.61±0.04	0.14±0.05	39.6	0.60±0.04	0.13±0.04	49.5
one minus power	$VE_i = 1 - (e^{-\beta_1 years_i{}^{\beta_2}})$	0.91±0.10	0.27±0.11	39.9	0.91±0.10	0.24±0.08	49.9
exponential	$VE_i = \beta_1 e^{-\beta_2 years_i}$	0.68±0.08	0.13±0.06	40.6	0.65±0.07	0.10±0.04	50.7
linear	$VE_i = \beta_1 - \beta_2 years_i$	0.64±0.07	0.06±0.03	41.2	0.62+0.05	0.04±0.02	51.3
one minus exponential	$VE_i = 1 - (\beta_1 e^{\beta_2 years_i})$	0.38±0.05	0.11±0.05	41.6	0.41±0.04	0.07±0.03	51.8
constant (no waning)	$VE_i = \beta_1$	0.51±0.03	NA	38.9	0.49±0.03	NA	54.2

2. VEhzcases by age (step 2)

To get vaccine efficacy estimates by age in years, we use data on number of HZ cases in the placebo and vaccinated group of the SPS trial for 5-year age groups, as reported by FDA[87]. To these data, the same models as before are fitted (Table 41), but with the $years_i$ variable replaced by a continuous age_j variable (j denoting the age at vaccination in years), and with parameters α_1 and α_2 to estimate instead of parameters β_1 and β_2. The values of the age variable are the midpoint of the 5-year age groups reported by FDA[87].

Comparing models:

Models are compared based on the deviance (since all models have the same number of parameters). Differences in deviance between all six models are small: no single model is clearly better than any of the other models (Table 41).

Table 38: Functions for how vaccine efficacy against number of herpes zoster cases changes with age at vaccination, maximum likelihood estimates of parameters and deviance values for models fitted on age-specific data from the Shingles Prevention Study.

function	$\alpha_1 \pm$ SE	$\alpha_2 \pm$ SE	deviance
one minus exponential	0.02 ± 0.01	0.04 ± 0.01	34.7
one minus power	13.76 ± 2.64	3.07 ± 0.62	34.7
linear	1.95 ± 0.29	0.02 ± 0.004	35.2
logarithmic	6.58 ± 1.24	1.43 ± 0.29	35.7
exponential	7.20 ± 4.14	0.04 ± 0.01	36.6
power	-10.26 ± 2.44	2.58 ± 0.58	37.2

3. VEhzcases by year after vaccination and age (step 3)

The previous paragraphs described different statistical models that are fitted to different sets of data. For each of these models, parameters are estimated. This paragraph describes how the 7 time-models (see step 1) can be combined with the 6 age-models (see step 2) to obtain an estimate for how HZ vaccine efficacy changes as a function of years since vaccination and age at vaccination combined.

This is illustrated for the exponential waning model with the age-model assuming a linear decrease in HZ vaccine efficacy with increasing age at vaccination. The same method is used for all other combinations of waning and age functions.

$VE_{HZcases}$ by age and year after vaccination ('$VE_{HZcases_{ij}}$') is obtained as follows:

$VE_{ij} = \beta_{1j} * e^{-\beta_2 * years_i}$, with and i=year after vaccination and j=age at vaccination.

With this equation we assume waning (how $VE_{HZcases}$ changes over time) to be the same for all ages j, which is reflected in a single parameter β_2 for all ages (estimated with in step 1). The age-specific parameter β_{1j} determines for each age j the $VE_{HZcases}$ the first year after vaccination. This parameter β_{1j} is obtained as follows:

$VE_{HZcases_j}$ for a certain age j estimated from step 2, is the average $VE_{HZcases_j}$ for that age over 3 years after vaccination, weighted according to the follow-up time for each year after vaccination:

$$VE_{HZcases_j} = \frac{w_1 * VE_{HZcases_{ij}}(i=1) + w_2 * VE_{HZcases_{ij}}(i=2) + w_3 * VE_{HZcases_{ij}}(i=3)}{w_1 + w_2 + w_3}$$

with w_1 to w_3 the total personyears of follow-up in the SPS trial for 1 to 3 years after vaccination. This is, we assume the relative follow-up time for each year after vaccination to be the same for the different ages. If we replace in this equation the terms '$VE_{HZcases_{ij}}(i=1)$' up to '$VE_{HZcases_{ij}}(j=3)$' by '$\beta_{1j} * e^{-\beta_2 * 1}$' up to '$\beta_{1j} * e^{-\beta_2 * 3}$' (exponential waning model), the only unknown parameter in the equation is β_{1j}, and can consequently be calculated for each age j.

By combining the 7 time-models (step 1) with the 6 age-models (step 2) we get 7*6=42 estimates for how VEhzcases changes as a function of time since vaccination and age at vaccination. It is unclear which of these models is most appropriate. Therefore, for the cost-effectiveness analyses, we will use for each age at vaccination considered (age 60-85), the estimates (i.e. the combination of age and time model) which result in the ICER most and least in favour of vaccination. As such, we cover the range of possible models and the impact they have on the cost-effectiveness of HZ vaccination.

VE_{BOI} BY YEAR AFTER VACCINATION

In contrast with number of HZ cases, BOI ('the herpes-zoster burden-of-illness-score') is not a count but a severity-by-duration measure of the total pain and discomfort associated with HZ. It is measured using the average SOIS for the vaccinated and placebo group. The latter may explain why the BOI score decreases by year after vaccination for the placebo group (Table 36): i.e. the follow-up time was not taken into account. And although the number of subjects decreases by year after vaccination, the follow-up time decreases faster by year after vaccination.

BOI can thus be seen as a mixture of distributions:

- the number of cases in the placebo and the vaccinated group have binomial distributions $B(N_{pl}, p_{pl})$ and $B(N_v, p_v)$ respectively, where N_{pl} and N_v represent the number of subjects in the placebo and vaccinated group, and p_{pl} and p_v are the expected proportions of cases under placebo and vaccine(Chang et al[45]).
- the severity scores for the cases, designated S_{pl1}, S_{pl2}, ...S_{plNpl} for the placebo group and S_{v1}, S_{v2}, ...S_{vNv} for the vaccinated group, are assumed to be mutually independent random variables with means μ_{pl}, μ_v and variance σ^2_{pl} and σ^2_v (Chang et al[77]).

As we do not have any information on the distribution (more specifically, the variances) of the severity scores for the cases (we could not get access to the original data), the only thing we can do is try to fit distributions to the given VE_{BOI} and confidence intervals for each year after vaccination. This is not straightforward as VE_{BOI} is skewed to the left, and therefore the distribution with best fit is a triangular one (with the published VE_{BOI} and the upper and lower confidence intervals being the most likely value, minimum and maximum respectively). As confidence limits are taken as minimum and maximum, the uncertainty of the VE_{BOI} estimates will be slightly underestimated. Disadvantage is that five independent different distributions will be used, one for the VE_{BOI} for each of the five years after vaccination. Clearly, such triangular distributions are far from optimal. Alternatively, we can assume the same waning rate as estimated for $VE_{HZcases}$. Note that VE_{BOI} should never be lower than the estimated $VE_{hzcases}$, as it accounts for the decrease in SOIS, in additional to the decrease in the number of HZ cases. Therefore, when the models estimate $VE_{hzcases}$ for a particular age at vaccination higher than the VE_{BOI} presented in Oxman et al[27] for the same age, the incidence estimate was used for that particular age at vaccination to approximate the burden-of-illness estimate. VE_{BOI} is not modelled separately for different age groups, because it was found not to differ significantly between the two age groups. We are aware of the fact that this approach is quite at hoc, but the 'best' we can come up with, given we do not have access to the original data.

How to assess the impact of the Zostavax® vaccine on the BOI (i.e. how to apply VE_{BOI})?

The BOI score for the Belgian population when not vaccinated, is calculated as described before (paragraph 0). By multiplying this score by (1-(VE_{BOI} *vaccine coverage)), we get the BOI score for the Belgian population when vaccinated ($BOI_{vacc\ i}$). Now, we need to know how this impacts on HZ-related costs and QALY's. As we modeled HZ-related costs and QALY's in function of the SOIS of a HZ case, we can assess impact of vaccination on costs and QALY's if we know the SOIS of a HZ case in the Belgian population when vaccinated (which will be lower than the SOIS of a HZ case in the Belgian population when not vaccinated, if the vaccine decreases severity and duration of HZ on top of preventing HZ cases). The SOIS of a HZ case in the vaccinated Belgian population, can be calculated as follows:

The formula for $BOI_{vacc\ i}$ is similar to the one from paragraph 0:

for each age i:

$$BOI_{vacc\_i} = \frac{SOIS_{vacc\_i} \times \#HZcases_{vacc\_i}}{total\ population_i}$$

with $BOI_{vacc\,i}$, $SOIS_{vacc\,i}$, respectively $\#HZcases_{vacc\,i}$, the BOI, the SOIS for a HZ case, respectively the number of HZ cases in the vaccinated Belgium population with age i, and $total\ population_i$, the number of people in Belgium with age i.

From this formula together with the formula from paragraph 0, it follows that:

$$SOIS_{vacc\_i} = \frac{(1 - (VE_{BOI} * coverage))}{(1 - (VE_{HZcases} * coverage))} * SOIS_i$$

This means that if VE_{BOI} = $VE_{HZcases}$, the SOIS of an average HZ case in vaccinated population is the same as the SOIS of an average HZ case when the population is not vaccinated. If VE_{BOI} > $VE_{HZcases}$, the SOIS of an average HZ case in vaccinated population is lower than the SOIS of an average HZ case when the population is not vaccinated. We assume that VE_{BOI} can never be smaller than $VE_{HZcases}$. This assumption would only be violated if the SOIS of an average HZ case is higher in the vaccinated versus the not-vaccinated group, which was not the case in the SPS trial. When VE_{BOI} is smaller than $VE_{HZcases}$, we assume VE_{BOI} to be equal to $VE_{HZcases}$.

Assessing the impact of vaccination on BOI like this, means that we are actually running the scenario using $VE_{HZcases}$, but accounting for the extra decrease in SOIS due to vaccination (only for the years after vaccination for which VE_{BOI} is bigger than $VE_{HZcases}$).

2.8.2.2 Intervention costs and HZ vaccine uptake

The marginal intervention costs consist of the purchasing costs as well as the marginal administration costs of the vaccine. The CDC price per dose of Zostavax® is $105.943 (€85.5, 10-pack, 1 dose vial) and $116.70 (€94.2, 1-pack, single dose 0.65mL vials); the private sector price per dose of Zostavax® is $153.93 (€124.3, 10-pack, 1 dose vial) and $161.50 (€130.4, 1-pack, single dose 0.65mL vials) (http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm#adult, accessed 21 June 2010). A price per dose of €90 is used, as this is likely to reflect the price for bulk purchase by a publicly funded program. Administration costs were set to €21.53, based on the cost of one GP consultation.

Vaccine uptake (or coverage) is assumed to be 30%, and to be the same for different ages and gender. It is varied in scenario analysis between 10% and 70%.

3 COST-UTILITY ANALYSIS: METHODS

3.1 VACCINATION OF ADULTS TO PREVENT HERPES ZOSTER

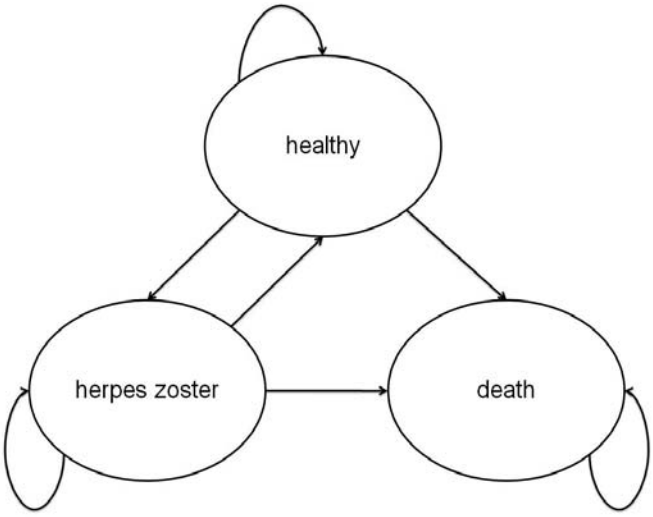
3.1.1 Main outcome

The main outcome of this health economic evaluation is the incremental cost-effectiveness ratio (ICER) of universal vaccination against Zostavax® versus no vaccination, and this for different age cohorts (60 up to 85).

3.1.2 Mathematical model structure

To get this outcome, a deterministic compartmental static model is constructed in R (http://www.r-project.org/). Individuals are modelled to get HZ according to their age in years. The vaccine is estimated to impact on the number of HZ cases, proportion getting post-herpetic neuralgia and deaths, as well as the severity and duration of HZ disease.

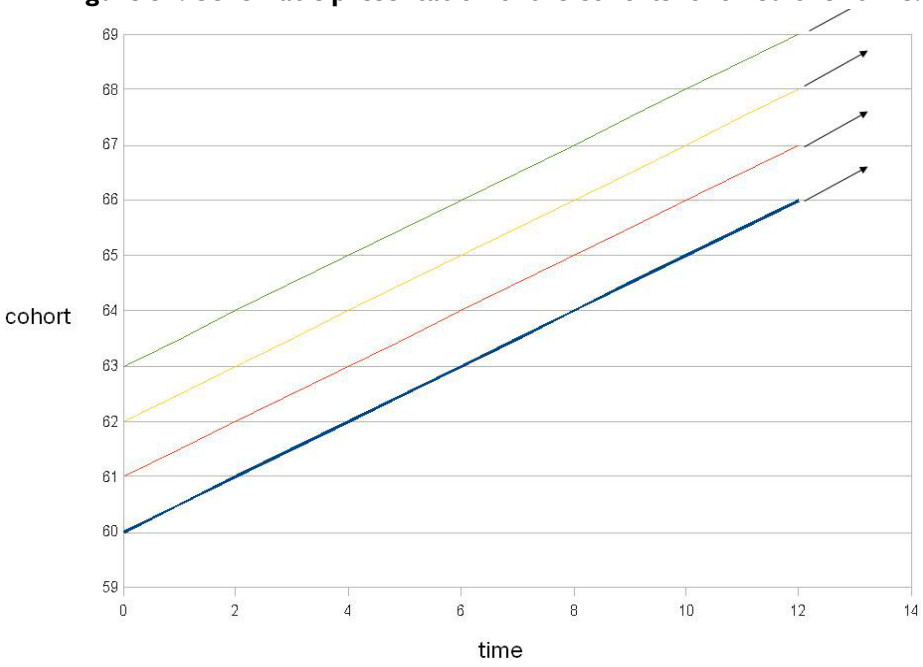
Figure 31: Basic structure of the static cohort model



Individuals belonging to a single age cohort are modelled to transition between the depicted states (Figure 31) in yearly cycles, until everybody is absorbed in the 'death state'.

Several ages cohorts are followed in time until all members of the cohort die (Figure 32). As such, the impact of vaccination at different ages can be investigated (e.g. only vaccinating at 60, vaccinating all people aged 60-65, and so on).

Figure 32: Schematic presentation of the cohorts followed over time.



This choice of model and structure is justified by the properties of HZ disease, as well as the properties of current HZ vaccine using the following argument: there is currently no convincing evidence that HZ vaccine would induce herd immunity,.

Instead of the half-cycle correction, the life table method is used to estimate state membership of the cohort model (Barendregt[86]).

3.1.3 Uncertainty and sensitivity analysis

The impact of uncertainty with respect to data source (e.g. should Scott et al[34] data or Drolet et al[46] data be used for the estimation of SOIS?) and model assumptions (e.g. which model should be used to estimate $VE_{HZcases}$?; or should additional efficacy against PHN cases and/or BOI be taken into account?), is assessed by repeating the analysis for the different possible data sources and model assumptions. So, for each set of choices on data source and/or model assumptions ('scenario's'), a new ICER (and uncertainty distribution) is generated. Both univariate and multivariate sensitivity analyses were done.

The uncertainty distribution of the ICER reflects the uncertainty from all input parameter (e.g. cost, SOIS, QALY loss) that were estimated based on a sample and not the complete Belgian population. Generally this sample size uncertainty ('parameter uncertainty') is quantified by assigning a distribution to each estimated parameter. Next, this uncertainty is propagated into the outcome (ICER) using MC method (1000 simulations), which results in an uncertainty distribution for the ICER[87]. However, taking parameter uncertainty into account becomes more troublesome when input parameters are modelled as a function of important covariates (e.g. age)[87]. In such case, uncertainty surrounding the function, not only a point value has to be quantified. Difficulties arise if for instance the distribution of the dependent variable (i.e. the input parameter like cost, SOIS) is not a member of the exponential family, if the dependent variable is transformed in a non-linear way, if the relationship between the covariate and the dependent variable is not linear, and/or if the model is semi- or non-parametric. Almost all of our models suffer from these problems, so that taking into account parameter uncertainty appropriately is impossible or would take serious amount of time. On the other hand, not taking into account important covariates could lead to false conclusions. For instance, if we would assume HZ related QALY loss to be independent of age, we might overestimate the benefit of the vaccine for younger ages and underestimate it for older ages. This is why currently parameter uncertainty is not taken into account for these models (hence, no CEAC's, cost-effectiveness planes or tornado graphs can be presented).

However, note that for almost all of the input parameters modelled as a function of covariates, the data source on which the models are built, and/or the models itself are uncertain, and that this data source and model uncertainty is taken into account. As parameter uncertainty is conditional on this data source and model uncertainty, including it would further increase the uncertainty surrounding the ICER's.

All analyses are done in R (http://www.r-project.org/) or @Risk (an add-in for Excel).

3.1.4 Overview tables of the estimated and assumed input parameters for the HZ model

Table 39 up to Table 45, and Figure 39 contain the parameter values used as input for the HZ model, as well as the data sources and models on which these values are based.

- Belgian demography: Table 39
- HZ related health care use: Table 39
- HZ related SOIS and QALY loss: Table 40
- HZ related costs: Table 40
- PHN related parameters: Table 44
- Parameters for immunocompetent population only: Table 45
- Vaccine coverage and cost: Table 40
- Vaccine efficacy: Figure 39

Table 39: Belgian demography and HZ health care use: Overview of the parameter values used as input for the cohort model, as well as the data sources and models on which they are based. The last column 'scenario' indicates if uncertainty surrounding the parameter is explored in scenario analysis (N=no, S=scenario analysis).

Input parameter	Age (yrs)	Assumption/ estimate	Data source	Model	Scenario
Belgian population		(by age)	Gompertz curve fitted on Belgian demographic data (BE)	by age in years	N
Life expectancy		(by age)	NIS 2007 (BE)	by age in years	N
Hospitalisation rate (per 1000)	60	0.17	MCD 2000-2007: ICD9 CM codes 053.0* in primary diagnostic field (BE)	GAM with age (in years) as covariate	N
	65	0.24			
	70	0.31			
	75	0.44			
	80	0.63			
	85	0.85			
Rate at least one GP visit (per 1000)	60	5.48	SIPH 2006-2008 (BE)	GAM with age (in years) as covariate	N
	65	6.42			
	70	7.44			
	75	8.84			
	80	10.75			
	85	12.87			
Mortality rate (per 1000)	<60	0	death certificates 1998-2007: ICD10 codes B01 and B02 in any cause of death (BE) + opinion 5 physicians: most likely [most or least in favor of vaccination]	point estimates by age (4 groups: <60, 60-74, 75-89, >89)	S
	60-74	0.0003 [0 or 0.0006]			
	75-89	0.0015 [0 or 0.0063]			
	>89	0.003 [0 or 0.0325]			
% hospitalised patient no GP visit		10.5%	NCSF survey hosp 2009 (BE)	independent of age	N

Table 40: HZ-related SOIS, QALY loss and costs, and vaccine coverage and price: Overview of the parameter values used as input for the cohort model, as well as the data sources and models on which they are based. The last column 'scen' indicates if uncertainty surrounding the parameter is explored in scenario analysis (N=no, S=scenario analysis).

Input parameter	Age (yrs)	Assumption/ estimate	Data source	Model	Scen
SOIS hospitalised patient	60	430	NCSF survey amb 2009 (BE)	Exponential, as a linear function of age (in years)	N
	65	465			
	70	499			
	75	533			
	80	567			
	85	601			
SOIS average HZ episode	60	29.79/248	Scott et al 2006/Drolet et al (accepted for publication)	Scott: Lognormal, as an exponential function of age (in years) and gender (correction for right-censoring)/Drolet: means for 4 age groups (<50, 50-59, 60-69, >69)	S
	65	33.26/ 250			
	70	37.14/ 250			
	75	41.47/ 333			
	80	46.31/ 333			
	85	51.71/ 333			
QALYs lost	*SOIS*		Scott et al 2006	Exponential, as a power function of SOIS (correction for right-censoring)	N
	29.8	0.12			
	41.5	0.15			
	51.7	0.17			
	250	0.44			
	333	0.52			
Total cost hospitalised patient	*SOIS*		NCSF survey hosp 2009 (BE)	Loglogistic, as a linear function of SOIS (correction for right-censoring)	N
	430	7990			
	465	8242			
	499	8493			
	533	8745			
	567	8996			
	601	9247			
Total cost ambulatory patient	*SOIS*		NCSF survey amb 2009 (BE)	Loglogistic, as a power function of SOIS(correction for right-censoring)	S
	29.8	108			
	41.5	121			
	51.7	134			
	250	370			
	333	429			
Vaccine coverage		30% (10-70%)	based on data for other vaccines (BE)	point estimate	S
Vaccine price/dose		€ 90	CDC	point estimate	S
Vaccine administration cost		€ 21.50	cost of one GP consultation (BE)	point estimate	N

Table 41: PHN: Overview of the parameter values used as input for the cohort model, as well as the data sources and models on which they are based. The last column 'scen' indicates if uncertainty surrounding the parameter is explored in scenario analysis (N=no, S=scenario analysis).

Input parameter	Age (yrs)	Assumption/ estimate	Data source	Model	scen
%HZ cases PHN	60	8	van Hoek et al 2009 (based on 7 studies on HZ related pain)	modelled transition between 4 pain states, parameters estimated using ML, proportion PHN as function of age (in years)	S
	65	10			
	70	13			
	65	17			
	80	23			
	85	31			
SOIS HZ episode no PHN	60	14.68/126.5	Scott et al 2006/ Drolet et al 2010	Scott: Lognormal, as an exponential function of age (in years) and gender /Drolet: means for 4 age groups (<50, 50-59, 60-69, >69)	S
	65	15.62/180.7			
	70	16.62/180.7			
	65	17.68/149.6			
	80	18.81/149.6			
	85	20.01/149.6			
SOIS hospitalised patient no PHN	60	166	NCSF survey amb 2009 (BE)	Exponential, as a linear function of age (in years), phn (yes or no)	N
	65	173			
	70	181			
	65	188			
	80	195			
	85	203			
SOIS hospitalised patient PHN	60	874			
	65	881			
	70	889			
	65	896			
	80	903			
	85	911			
SOIS HZ episode PHN[1]	49-60	542.1	Drolet et al 2010	means for 4 age groups (<50, 50-59, 60-69, >69)	N
	61-70	733.4			
	>70	787.5			

[1]Scenario using SOIS Scott et al: SOIS HZ episode PHN is obtained by multiplying SOIS HZ episodes no PHN by Drolet SOIS PHN/Drolet SOIS no PHN

Table 42: Immunocompetent population (IMM): Overview of the parameter values used as input for the cohort model, as well as the data sources and models on which they are based. The last column 'scen' indicates if uncertainty surrounding the parameter is explored in scenario analysis (N=no, S=scenario analysis).

Input parameter	Age (yrs)	Assumption/ estimate	Data source	Model	scen
% HZ hospitalised patients IMM	<60	63	NCSF survey hosp 2009 (BE)	4 age groups (<60, 60-69, 70-79, >79)	N
	60-69	41			
	70-79	60			
	>79	56			
% HZ ambulatory patients IMM	<60	52	NCSF survey amb 2009 (BE)	4 age groups (<60, 60-69, 70-79, >79)	N
	60-69	29			
	70-79	33			
	>79	38			
SOIS HZ episode IMM	60	21.50	Scott et al 2006	Lognormal, as an exponential function of age (in years) and gender (correction for right-censoring)	N
	65	24.00			
	70	26.80			
	65	29.92			
	80	33.40			
	85	37.30			
SOIS hospitalised HZ patient IMM		cfr. SOIS hospitalised HZ patients			

3.2 VACCINATION OF CHILDREN AGAINST PRIMARY VZV INFECTION

3.2.1 Main outcome

The main outcome of this part of the evaluation is the incremental cost-effectiveness ratio (ICER) of universal vaccination against primary varicella infection versus no vaccination.

3.2.2 Mathematical model structure

The transmission dynamic deterministic model used in this report was developed by van Hoek et al[66] based on that of Brisson et al[71]. This realistic age-structured (RAS) model assumes a steady age-specific death rate and a constant birth cohort.

The model structure is illustrated in the flow diagram in Figure 33.

People infected with VZV may develop disease and will develop immunity against VZV infection. After an average period of natural protection ($1/\delta$), VZV immune persons may become susceptible to herpes zoster. Then they can either develop HZ disease or be boosted by an infectious case, and consequently gain temporary protection against HZ. People vaccinated against HZ become zoster susceptible again after an average period of vaccine protection ($1/\delta_v$). It is assumed that individuals can experience only one episode of herpes zoster in their life.

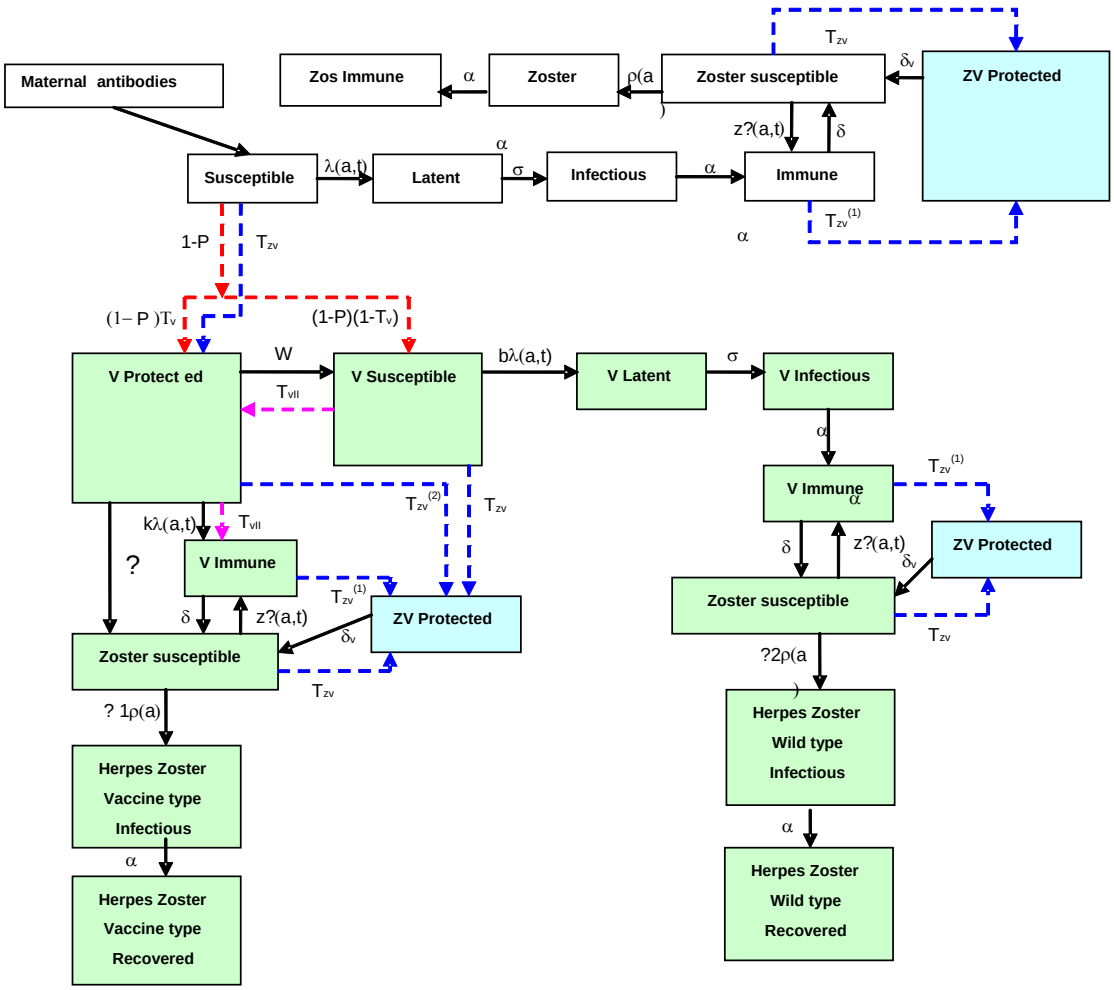
Individuals immunized against varicella-zoster can still develop zoster, though reportedly at a lower rate than naïve persons[1, 88]. The parameter π is the rate at which vaccinated people become susceptible to zoster and χ is the rate at which people develop zoster once susceptible to it.

For varicella and zoster vaccination parameters, we used the values estimated by van Hoek et al[66]. For simplicity, it is assumed that the susceptibility of vaccinated individuals

to become infected is the same as non-vaccinated people (b=100%). It is also assumed that vaccinated individuals are as likely as non-vaccinated people to be boosted by contact with a varicella case (k=100%).

A proportion (P) of individuals vaccinated against varicella remains susceptible (vaccine failure). A proportion (T) of those who respond (1-P) is protected from varicella infection: (1-P)*T. The proportion of individuals who respond but are still liable to be infected (breakthrough cases) if exposed is: (1-P)*(1-T). The parameter W is the rate at which the protection of the vaccine wanes. The responders (T) to a second dose of varicella vaccine are assumed to be fully protected for life.

Figure 33: Flow diagram of the dynamic model.



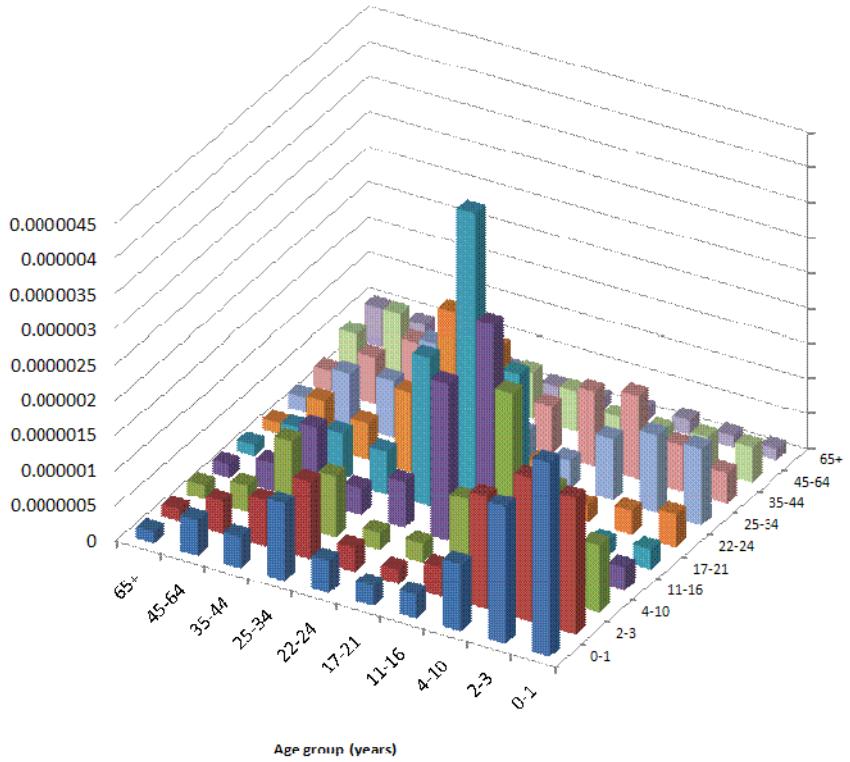
Herpes zoster vaccination
1st dose varicella vaccination
2nd dose varicella vaccination

1. In case of ?<?v, people will remain in the immune compartment although they are vaccinated against HZ
2. In case of ?< ?v people will remain in the immune compartment although they are vaccinated against HZ

P = initial vaccine failure
T_v = Take first vaccine dose varicella
T_{vll} = Take second vaccine dose varicella
α = Duration of infectious period
ρ(a) = Reactivation rate
? = Progression rate from vaccine protected to zoster susceptible
? = force of infection
k = probability to be boosted after contact when you are vaccine protected
? = Change in zoster reactivation rate in varicella vaccinees
z = probability to be boosted after contact when you are zoster susceptible
σ = Duration of latency (rate to become infectious)
W = Waning rate

The mean pattern of close contacts estimated for Belgium (see data section above) and described in detail in previously published papers by Hens et al[29] is shown in simplified form in Figure 34. Here, the ages (years) are grouped in 10 intervals: 0-1, 2-3, 4-10, 11-16, 17-21, 22-24, 25-34, 35-44, 45-64 and 65+.

Figure 34: Age-specific social contact rates by age groups (per person per year) using information on close contacts during more than 15 minutes.



In the dynamic transmission model, the transmission of the virus is assumed to be proportional to contact rates, as described in Wallinga et al[89], Ogunjimi et al[31], and Goeyvaerts et al[90]. The analyses using the dynamic transmission model are conducted using Berkeley Madonna, Matlab and R.

3.2.3 Fitting to Belgian data

The best model fit to the Belgian seroprevalence data is shown in Figure 35, along with the corresponding force of infection (i.e. the per-susceptible rate of infection, see Hens et al[40]).

Figure 35: Model fit of the age-specific seroprevalence of varicella-zoster infections in Belgium, and associated force of infection.

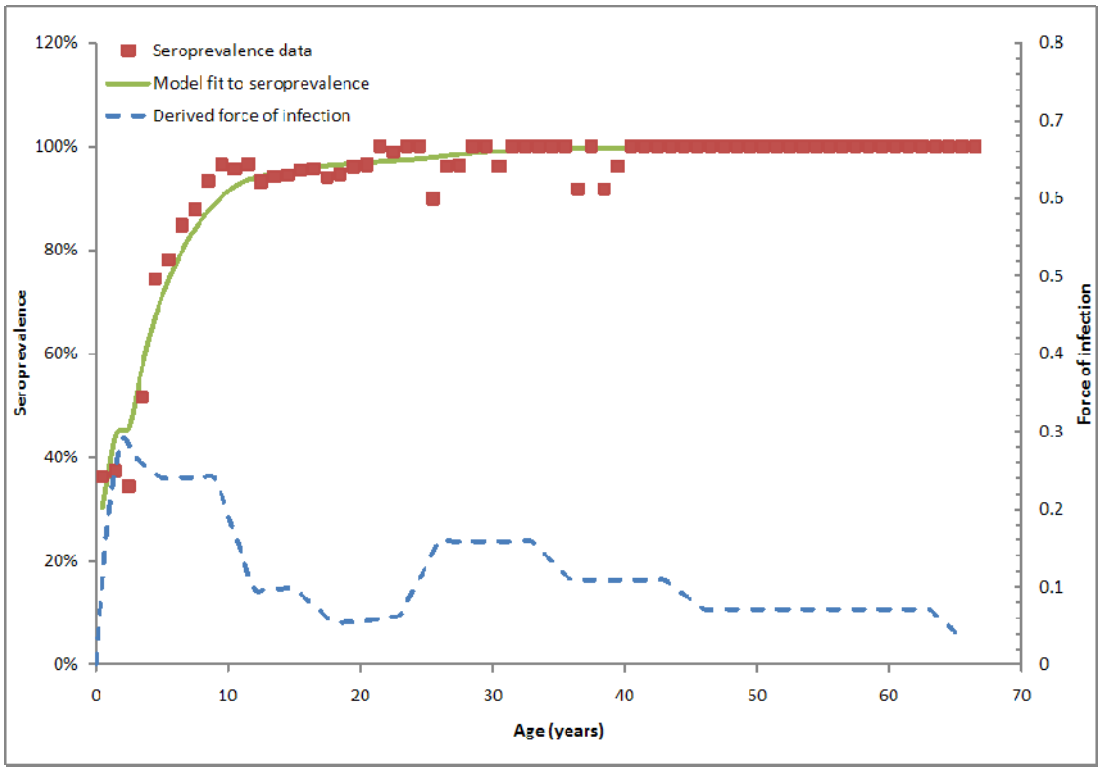
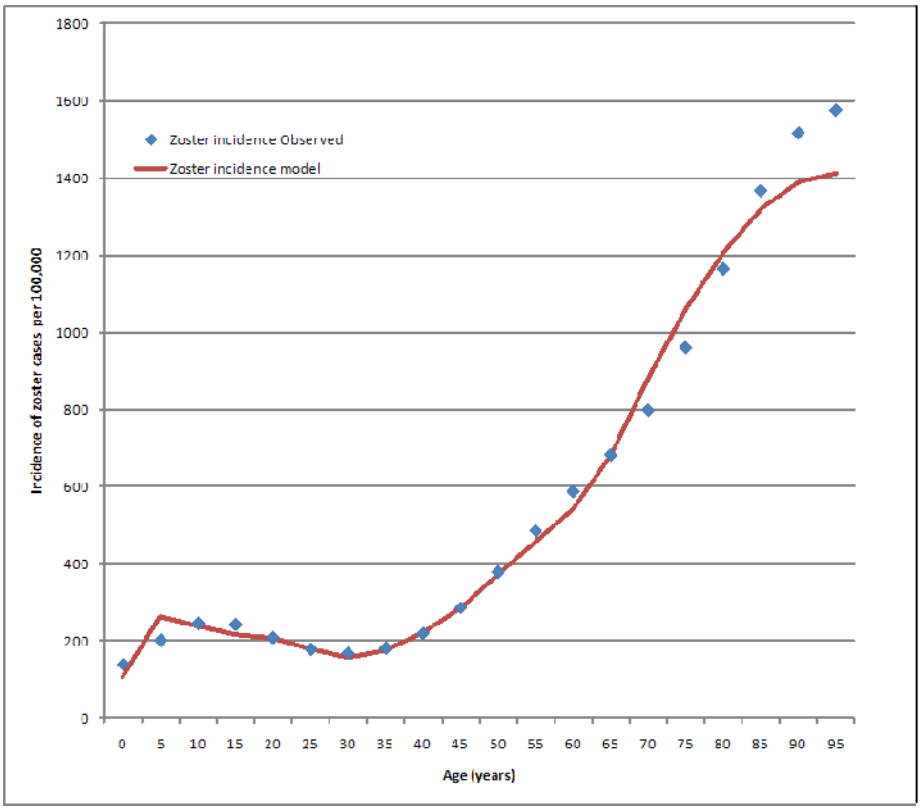


Figure 41 shows that the pre-vaccination force of infection is highest among young children and shows a secondary maximum between ages 25 and 45, during ages when adults are living with young children in the household (this age-specific pattern mimics the contact frequency we can observe in the social contact studies (cf. figure 40; Hens et al[29]).

The age-specific reactivation rate ($\rho(a)$) was fitted to the zoster incidence data given the transmission matrix and the assumptions about the duration of boosting after exposure to natural CP (see Brisson et a[91]). The model fit of the zoster incidence is shown in Figure 36.

Figure 36: Model fit of the age-specific incidence of zoster in Belgium.



3.2.4 Options for childhood VZV (CP) vaccination

There are many options for childhood VZV vaccination conceivable in Belgium, but for the sake of simplicity we only present the results of a number of pivotal options in this report:

1. No vaccination
2. 1 dose of VZV vaccine at age 1, at 95% coverage
3. 2 doses of VZV vaccine at ages 1 and 4 years, at coverage 95% and 90%;
4. 2 doses of VZV vaccine at ages 1 and 6 years, at coverage 95% and 90%;
5. 2 doses of VZV vaccine at ages 1 and 11 years, at coverage 95% and 80%;
6. 2 doses of VZV vaccine at ages 1 and 11 years at coverage 95% and 80% combined with 1 dose of HZ vaccine at age 60 years at 30% coverage;

Variations on these options, such as the inclusion of a catch-up program, other potentially achievable coverage rates, and other combinations with HZ were also explored, but were not found to be relevant to add to this report. Note also that the option of single dose vaccination is currently considered purely theoretical, since it is not considered a defensible option by the Superior Health Council.

3.2.5 Overview tables of the estimated and assumed input parameters for the VZV model

Table 43, Table 47 and Figure 37 contain the parameter values used as input for the VZV model, as well as the data sources and models on which these values are based.

Table 43: Estimated/assumed input parameters for the dynamic VZV model, as well as data sources and models on which estimates/assumptions are based. See Figure 33 for explanation of each input parameter. The last column 'scen' indicates if uncertainty surrounding the parameter is explored in scenario analysis (N=no, S=scenario analysis).

Input parameter	Assumption/estimate	Data source	Model	Scen
Maternal antibody waning	2 per year (=6 months)	van Hoek et al 2011		N
lambda	see Figure 34 and Figure 35	based on Belgian contact matrix (BE)	See Ogunjimi et al and Goeyvaerts et al	N
sigma	365/14 per year (=14 days)	Beneson 1995		N
alpha	365/7 per year (=7 days)	Beneson 1995		N
delta	1/20 per year (=20 years) [7.5 or 42 yrs]	Brisson et al 2002 (Vaccine)		S
z	0 or 100%	assumption		N
b	100%	van Hoek et al 2011		N
rho	(by age, see Figure 37)	based on lambda, delta and belgian HZ incidence data	Van Hoek et al 2011: depends on lambda, delta and HZ incidence	S
P	4%	Brisson et al 2000 (Epi&Inf)		N
Tv	1 [0.9936 or 0.932346]	van Hoek et al 2011	depends on waning	S
TvII	1 [0.999671 or 0.98621]	van Hoek et al 2011	depends on waning	S
w1	22.54 [14.82 or 67.58]	van Hoek et al 2011	depends on take	S
w2	74.26 [38.04 or 199.78]	van Hoek et al 2011	depends on take	S
chi1=chi2	0.061421935 [0.030163967 or 1]	van Hoek et al 2011	depends on w1, w2, Tv, TvII and delta	S
k	0 or 100%	assumption		N
Tzv	age 60-64:0.77	van Hoek et al 2011	age-specific, depends on delta and deltav and CTR data (Tzv shown here assuming delta=1/20 and deltav=1/7.5)	S
	age 65-69:0.68			
	age 70-74:0.49			
	age 75-79:0.42			
	age 80-84:0.18			
	age 85+:0.07			
deltav	1/7.5 per year (=7.5 years) [3.6 or 100 yrs]	van Hoek et al 2011		S
pi	1/20 per year (=20 years)	van Hoek et al 2011		N

Figure 37: Age-specific HZ reactivation rate, used as input for the VZV dynamic model, for different assumption on duration of natural boosting.

Table 44: Estimated/assumed input parameters for the economic part of the VZV model, as well as data sources and models on which estimates/assumptions are based.

Input parameter	Assumption / estimate	Data source	Model
Rate CP at least 1 GP visit	by age (Figure 15)	SIPH 2006-2008 (BE)	observed data, a single rate for age group 13 and older (because of few events)
Rate CP hospitalisations	by age (Figure 13)	MCD 2000-2007: ICD9 CM codes 052.* in primary diagnostic field (BE)	observed data, a single rate for age group 5-12 and 13 and older (because of few events)
% hospitalised patient no GP visit	18	NCSF survey hosp 2009 (BE)	expected value of beta distribution
#patients at least 1 GP visit/#patients no medical care	0.79	Child&Family survey 2010 (BE)	assumed to be 0 for age 13 and older
#patients at least 1 GP visit/#patients only pediatrician	0.29	Child&Family survey 2010 (BE)	expected value of beta distribution
Case fatality rate (per 100,000)	age<5:0.08	Brisson and Edmunds 2003	
	age 5-14:0.02		
	age 15-44:0.04		
	age 45-64:0.03		
	age>64:0.11		
Total cost hospitalized patient	2870	NCSF survey hosp 2009 (BE)	expected value of lognormal distribution
Total cost ambulatory patient	39	NCSF survey amb 2009 (BE)	expected value of shifted loglogistic distribution
Total cost patient not seeking medical care	€ 0	NCSF survey amb 2009 (BE)	point value
QALY loss hospitalized patient	0.017	Child&Family survey 2010 (BE)	point value
QALY loss ambulatory patient/no medical care	0.010/0.004	Child&Family survey 2010 (BE)	expected value of exponential distributions, with consulting any physician (yes/no) as covariate
Burden VB compared to VP	50%	Based on Chaves et al 2008	point value (varied between 10%-90% in scenario analysis)

4 COST-UTILITY ANALYSIS: RESULTS

4.1 VACCINATION AGAINST HZ: RESULTS

4.1.1 Clinical and economic impact of HZ vaccination

Clinical and economic impact of HZ vaccination is shown in Table 45 for a scenario most and least in favour of vaccination. As indicated above, substantial uncertainty exists with respect to which estimate or assumption to choose for five input parameters (SOIS, HZ-related deaths, vaccine efficacy endpoint, waning of vaccine efficacy according to age at vaccination and immunocompetence of the target population). Therefore we consider a scenario in which for these five parameters the estimate or assumption least in favour of vaccination is chosen, and a scenario for which the estimates or assumptions for these five parameters most in favour of vaccination are chosen. This is described in detail in the next paragraphs.

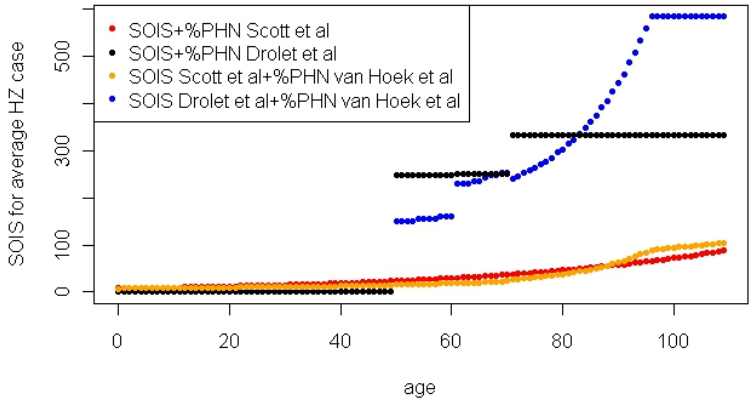
The five input parameters are the following:

1.Age-specific SOIS for an average HZ case (Figure 38), two possible choices:

- Age-specific estimate based on Scott et al study ('Scott SOIS')
- Age-specific estimate based on Drolet et al[46] study ('Drolet SOIS')

One could also assume age-specific estimates based on either Drolet et al or Scott et al, separately for PHN and non-PHN HZ cases, weighted according to the age-specific proportion HZ cases with PHN obtained by van Hoek et al[43] (based on 7 studies) (Figure 38). However, exploratory analyses indicated that assuming Scott SOIS (without weighing) results in the scenario least in favour of vaccination and assuming Drolet SOIS (without weighing) results in the scenario most in favour of vaccination. Therefore only these two choices are further considered.

Figure 38: Age-specific SOIS for an average HZ case, based on Scott et al data, Drolet et al data, Scott et al data weighted according to proportion HZ cases having PHN from van Hoek et al, and Drolet et al data weighted according to proportion HZ cases having PHN from van Hoek et al.



2.Annual HZ related deaths, 3 possible choices:

- Minimum (none)
- Most likely (all registered deaths with HZ as a cause for which at least 4 of the 5 clinicians agreed they are due to HZ)
- Maximum (all registered deaths with HZ as a cause, except for the ones for which at least 4 of the 5 clinicians agreed they are not due to HZ)

3.Vaccine efficacy, 2 possible choices:

- Against number of HZ cases
- Against burden-of-illness (including protection against number of cases as well as disease duration and severity)

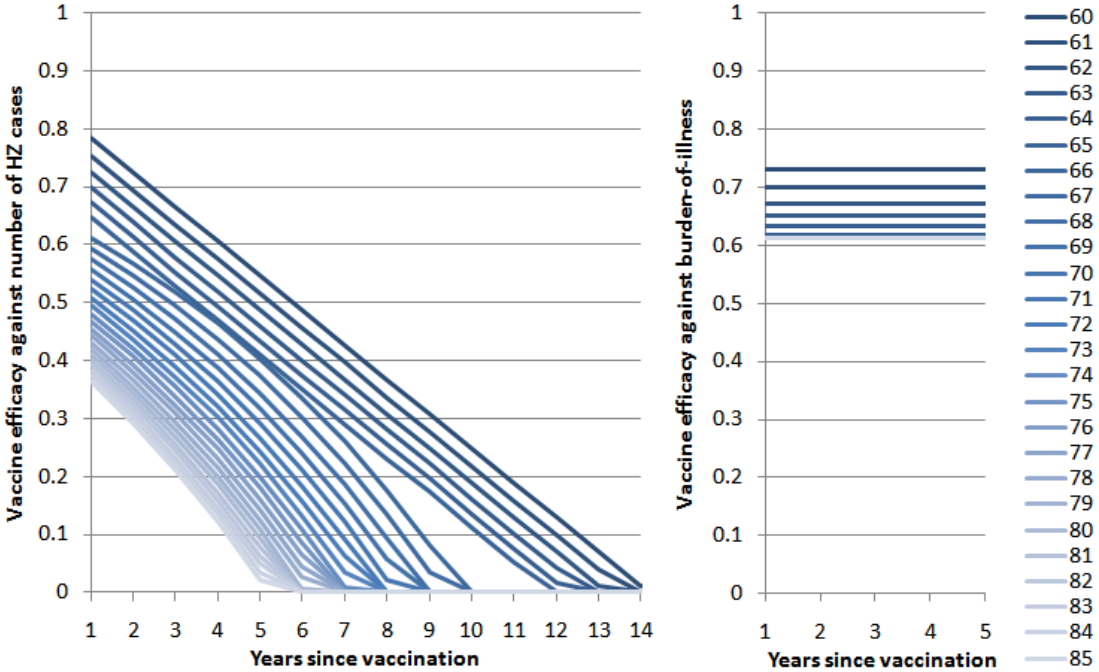
As PHN is defined in terms of duration (at least 3 months) and severity (pain of at least score 3) of HZ disease, estimates for efficacy in preventing PHN are not used, as such prevention is already incorporated in the estimates for VE_{BOI}. Note that VE_{BOI} only takes into account the duration and severity of HZ disease for the first 6 months after rash onset.

4.Waning of efficacy according to age at vaccination: 42 possible choices (i.e. 42 combinations of time and age models):

We show results using for each age at vaccination considered (ages 60-85), the combination of time- and age-model which result in the scenarios most and least in favour of vaccination (as assessed by prior analyses).

- Models most in favour of vaccination: No waning combined with age-model most in favour of vaccination (Figure 39, right panel (for VE_{BOI}))
- Models least in favour of vaccination: Fastest estimated waning combined with age-model least in favour of vaccination (Figure 39, left panel (for $VE_{hzcases}$))

Figure 39: Estimated vaccine efficacy over time (X-axis) and by age at vaccination (different lines) used as input for the scenario least in favour (left panel), and most in favour (right panel) of vaccination. For details see Bilcke et al, Vaccine 2012.



5.Population that can benefit from the vaccine, 2 possible choices:

- Everybody
- Only the immunocompetent population

In our opinion it is not clear which set of choices represent the most likely scenario, and therefore we will present a scenario most and least in favour of vaccination, rather than a base case scenario.

Scenario most in favour of vaccination:

- Drolet SOIS
- Maximum number of HZ deaths
- Taking additional efficacy against burden-of-illness into account
- Assume for each age at vaccination, no waning of vaccine efficacy and age model most in favour of vaccination
- Assume everybody can benefit from the vaccine (and not only the immunocompetent population)

Scenario least in favour of vaccination:

- Scott SOIS
- Assuming no HZ related deaths can be prevented by the vaccine
- Only taking into account efficacy against number of HZ cases
- Assume for each age at vaccination, fastest waning of efficacy and age model least in favour of vaccination
- Assume only immunocompetent population can benefit from the vaccine

There is a general trend for less potential avoidable burden with increasing age at vaccination of the cohorts (indicated in the headings: cohort 60 is vaccinated at age 60 and followed until death, whereas cohort 65 is vaccinated at age 65 and followed until death) (Table 45). The main reasons for this are twofold: (1) there are fewer people alive at older ages of vaccination, and fewer life years during which benefits can be obtained from vaccination; (2) vaccine efficacy is lower in older vaccine recipients.

Table 45: Avoided disease and economic burden through HZ vaccination of different age cohorts over their lifetime, for a scenario most and least in favour of vaccination. Measures involving discounted costs (3%) and effects (1.5%) are marked by a '(d)'.

	scenario	cohort 60	cohort 70	cohort 80	cohort 85
Avoided HZ cases	most	3,515	1,478	374	142
	least	701	315	82	19
Avoided HZ hospitalizations	most	178	87	25	10
	least	21	9	4	1
Avoided PHN cases	most	678	373	135	64
	least	74	51	22	7
Avoided HZ deaths	most	1.22	0.79	0.35	0.19
	least	0	0	0	0
Avoided HZ life-years	most	9	5	1	1
	least	0	0	0	0
Avoided disease-related costs (€)	most	2,931,474	1,475,147	521,302	225,881
	least	221,760	106,148	38,070	9,449
Total vaccine cost (€)	most	3,697,485	2,791,266	1,467,991	818,296
	least	3,697,485	2,791,266	1,467,991	818,296
Incremental costs (€)	most	766,011	1,316,119	946,690	592,415
	least	3,475,725	2,685,117	1,429,921	808,847
Incremental costs (€) (d)	most	1,759,838	1,669,711	1,026,773	619,514
	least	3,505,428	2,695,159	1,432,193	809,239
Incremental QALYs	most	1,725	833	280	120
	least	77	39	11	3
Incremental QALYs (d)	most	1,406	728	257	113
	least	72	37	11	3
Cost (€) per prevented HZ case (d)	most	609	1,292	2,990	4,642
	least	5,368	8,972	18,096	43,969
Cost (€) per life-year gained (d)	most	260,071	402,474	711,205	1,069,356
	least	NA	NA	NA	NA
Cost (€) per QALY gained	most	444	1,580	3,380	4,927
	least	45,160	69,689	128,003	297,141
Cost (€) per QALY gained (d)	most	1,251	2,294	3,988	5,498
	least	48,978	73,513	132,220	303,705

HZ: herpes zoster, PHN: post-herpetic neuralgia, QALY: quality-adjusted life-year, NA: not applicable (because no avoided life-years).

4.1.2 Cost-utility of HZ vaccination

Table 45 also shows the cost per prevented HZ case, the cost per lifeyear gained, and the cost per QALY gained for vaccination of different age cohorts. For both scenarios most and least in favour of vaccination, a discount rate of 3% for costs and 1.5% for effects is assumed, the vaccine is assumed to cost €90/dose (see p.66), and the health care payer perspective is taken.

Vaccination is valued to be cost-effective for all age cohorts considered in the scenario most in favour of vaccination, but for none of the age cohorts in the scenario least in favour of vaccination. This large difference between the scenarios most and least in favour indicates that the estimate or assumption chosen for (some of) the five input parameters (SOIS, HZ-related deaths, vaccine efficacy, waning of vaccine efficacy and population that can benefit from the vaccine), has a substantial impact on the cost-utility of HZ vaccination. This is explored in the next paragraphs.

4.1.2.1 Univariate scenario analysis.

For each of the five input parameters separately (SOIS, HZ-related deaths, vaccine efficacy, waning of vaccine efficacy and population that can benefit from the vaccine), the scenarios most and least in favour of vaccination are run again, altering the estimate/assumption for this particular input parameter (Figure 40 and Figure 41).

Figure 40: Incremental cost per Quality-Adjusted Life-year (QALY) gained (ICER) of vaccinating against HZ compared to not vaccinating, for age cohorts 60 up to 85. Results of a univariate scenario analysis based on the scenario most in favour of vaccination: scenarios are shown in which a single estimate or assumption is changed into the estimate or assumption least in favour of vaccination.

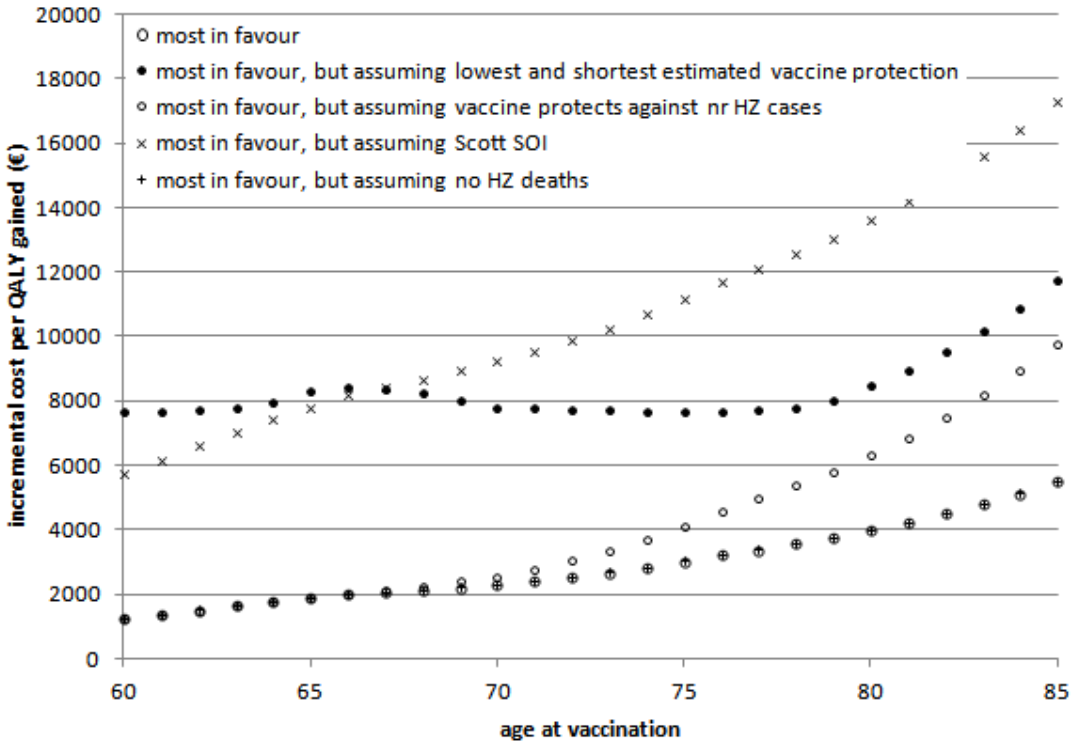
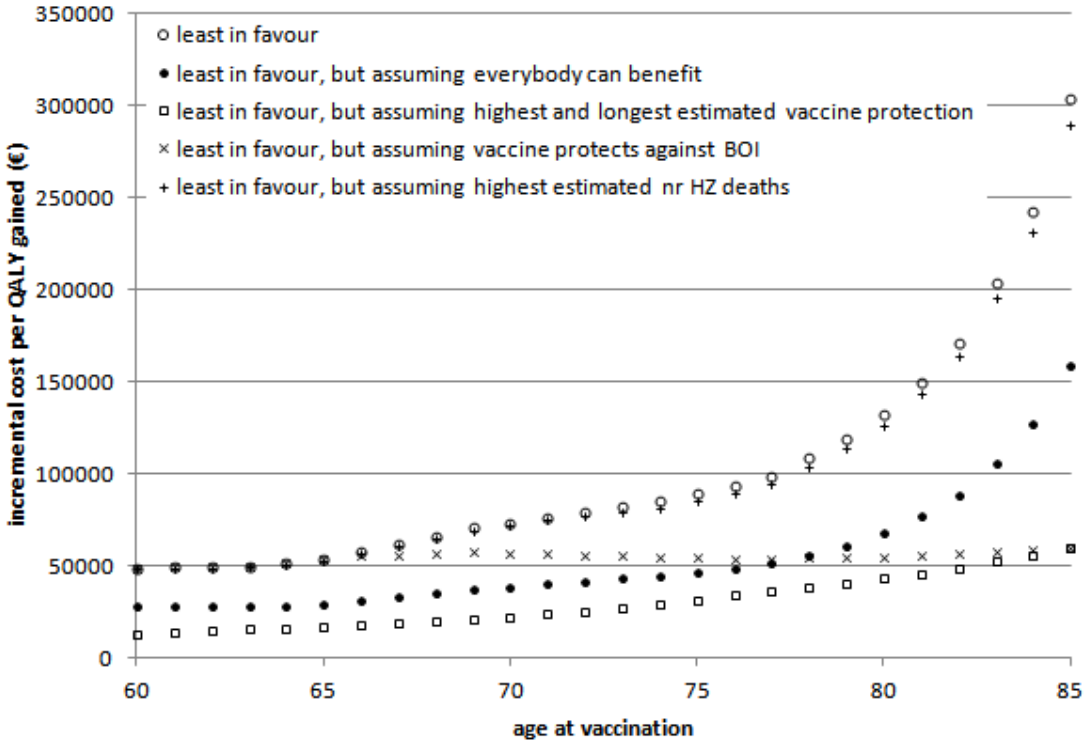


Figure 41: Incremental cost per Quality-Adjusted Life-year (QALY) gained (ICER) of vaccinating against HZ compared to not vaccinating, for age cohorts 60 up to 85. Results of a univariate scenario analysis based on the scenario least in favour of vaccination: scenarios are shown in which a single estimate or assumption is changed into the estimate or assumption most in favour of vaccination.



Input parameters which impact most on the age at which HZ vaccination is most cost-effective, as assessed by univariate scenario analysis.

In most scenario's (so for most of the combinations of estimates and assumptions for the five input parameters), the younger the cohort vaccinated, the more cost-effective this vaccination. However, for the following combination of estimates and assumptions, this is not true.

If the additional efficacy against burden of illness is taken into account, and fastest vaccine waning is assumed. This is the case in following two scenario's:

a. Scenario most in favour, but assuming fastest estimated waning instead of slowest estimated waning (Figure 40: 'most in favour, but assuming lowest and shortest estimated vaccine protection)

b. Scenario least in favour, but taking into account additional efficacy against burden-of-illness (Figure 41: 'least in favour, but assuming vaccine protects against BOI').

Input parameters which impact most on the cost-effectiveness of HZ vaccination, as assessed by univariate scenario analysis.

Figure 40 and Figure 41 show clearly that the input parameter which influences the most the most and least in favour cost per QALY gained (ICER), depends on the age cohort. For the youngest cohorts, the assumption on duration of vaccine protection (assuming no waning or fastest estimated waning) changes the most and least in favour ICER the most. For the older cohorts, the most in favour ICER increases most when assuming average HZ-related SOIS based on Scott et al rather than Drolet et al[46]. The least in favour ICER decreases most for the oldest cohorts (age 81-85) if extra efficacy against burden of illness is taken into account.

However, note the assumption on the population which can benefit from the vaccine (everybody or only immunocompetent persons) could not be investigated with univariate sensitivity analysis for the scenario most in favour of vaccination, as Drolet and colleagues did not publish SOIS estimates for immunocompetent and immunocompromised HZ patients separately. Also, univariate scenario analysis can not reveal how ICER changes by changing the estimates and assumptions of several input parameters simultaneously. This is why in the next paragraph, multivariate scenario analysis is performed.

4.1.2.2 Multivariate scenario analysis.

To avoid running an excessive number of scenario's, we restrict the multivariate sensitivity analysis to altering simultaneously the assumption on SOIS (Scott SOIS or Drolet SOIS), waning of the vaccine and the population that can benefit from the vaccine. The focus now is on absolute ICER values, not on how it depends on age cohort (which is already discussed in the previous paragraph). The other input parameters are fixed because of the following reasons:

- The number of HZ related deaths is fixed (at no deaths), as univariate analysis showed it influences ICER very little (Figure 40).
- We assume that the vaccine only protects against cases (VEhzcases). Assuming additional efficacy against burden-of-illness only influences the ICER for older age cohorts substantially, the ICER for the youngest age cohorts considered, stays the same. As the focus is now on effect on absolute ICER values, not on how it depends on age cohort, we only consider scenario's taking vaccine protection against the number of HZ cases into account.

The result of the multivariate sensitivity analysis is shown in Figure 42 and discussed hereafter.

Input parameters which impact most on the cost-effectiveness of HZ vaccination, as assessed by multivariate scenario analysis.

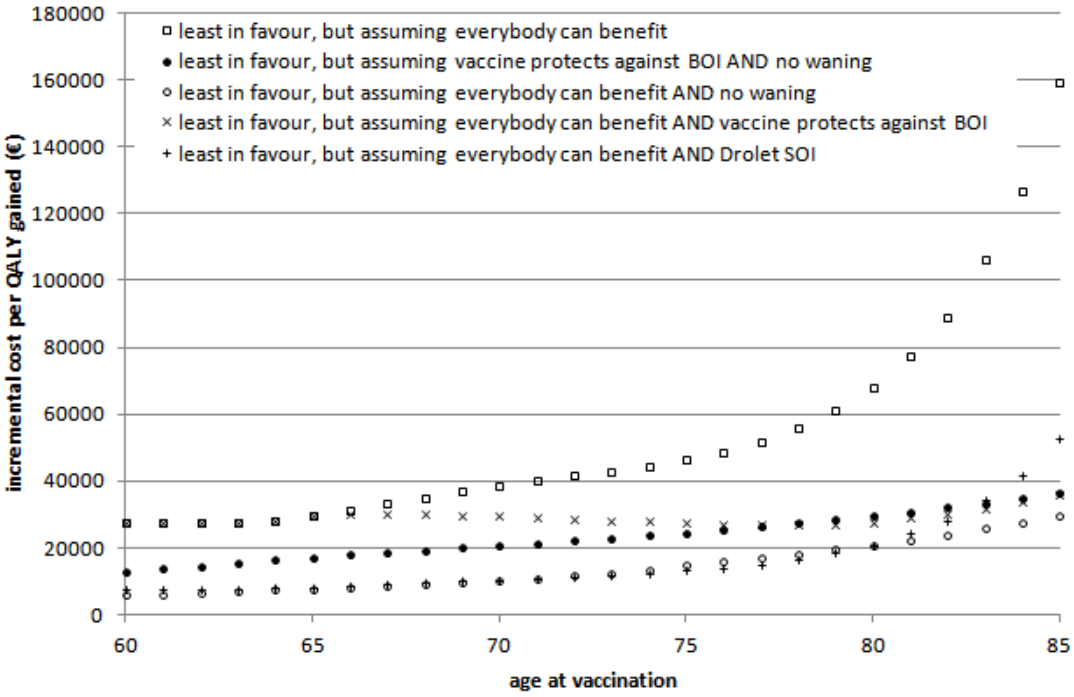
SOIS - Assuming SOIS based on Drolet et al[46] results in an ICER <€30000/QALY for all cohorts until 82, no matter which assumption for the duration of vaccine protection (waning) (Figure 42).

Duration of protection - No matter which SOIS or population that can benefit from the vaccine is assumed, if assuming no waning, then HZ vaccination is cost-effective (ICER <€30000/QALY) for the age cohorts 60-79 (Figure 42).

Immunocompetent – Assuming the vaccine only can protect the immunocompetent population, results in an ICER <€30000/QALY for cohorts 60-79 (no waning of efficacy assumed).

Age cohort - Vaccination of age cohort 60 until and including 65 is found to be cost-effective for all scenario's except the ones assuming fastest estimated waning combined with SOIS based on Scott et al.

Figure 42: Incremental cost per Quality-Adjusted Life-year (QALY) gained (ICER) of vaccinating against HZ compared to no vaccination, for age cohorts 60 up to 85. Results of a multivariate scenario analysis based on the scenario least in favour of vaccination: scenarios are shown in which more than one estimate or assumption is changed into the estimates or assumptions most in favour of vaccination.



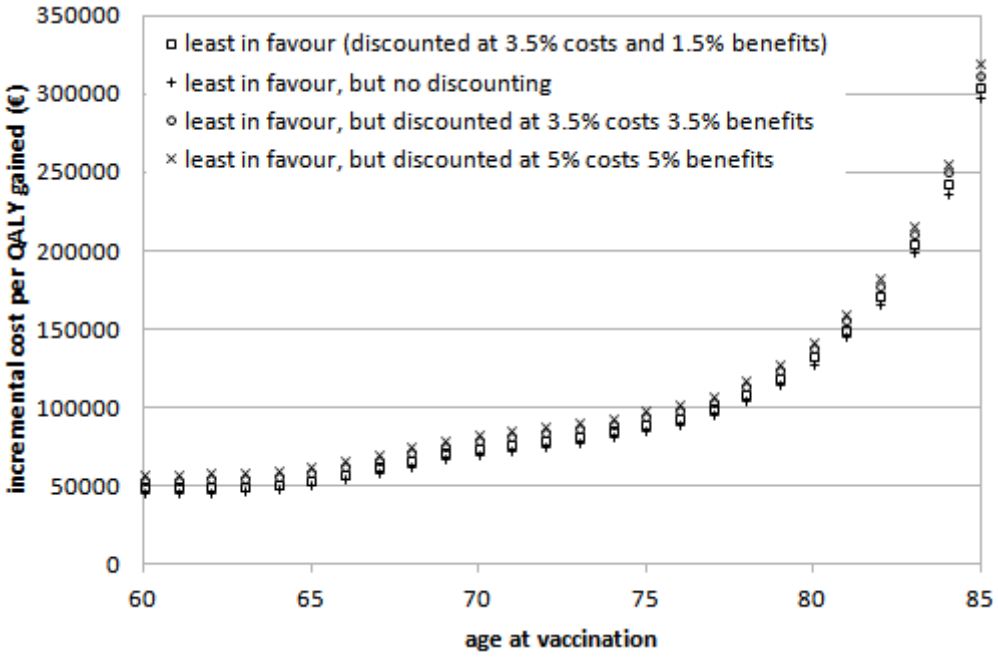
4.1.2.3 *About methodological, data source, model and parameter uncertainty.*

The above described uncertainty around SOIS, vaccine efficacy and waning, and the population possibly protected by the vaccine reflects different methodological, data source and model choices. From Figure 40 through Figure 42 it is clear that this uncertainty influence the cost-effectiveness of HZ vaccination substantially, and that this is more so the older the age of the cohort that is vaccinated. As parameter uncertainty is conditional on methodological, data source and model uncertainty[87], including it would further increase the uncertainty surrounding the cost per QALY gained. (But because of the reasons explained on p.68, parameter uncertainty is not explicitly quantified in the current analysis).

4.1.2.4 *Discount rate.*

The influence of the discount rates on the cost per QALY gained is limited, in comparison with some other vaccination programmes. This is illustrated in Figure 43 for some prevailing choices of discount rates. It is clear that the impact of discounting leaves the choice of preferred strategy unchanged.

Figure 43: Incremental cost per Quality-Adjusted Life-year (QALY) gained (ICER) of vaccinating against HZ compared to not vaccinating, for age cohorts 60 up to 85. Results of a univariate scenario analysis based on the scenario least in favour of vaccination: scenarios are shown for different discount rates of costs and benefits.



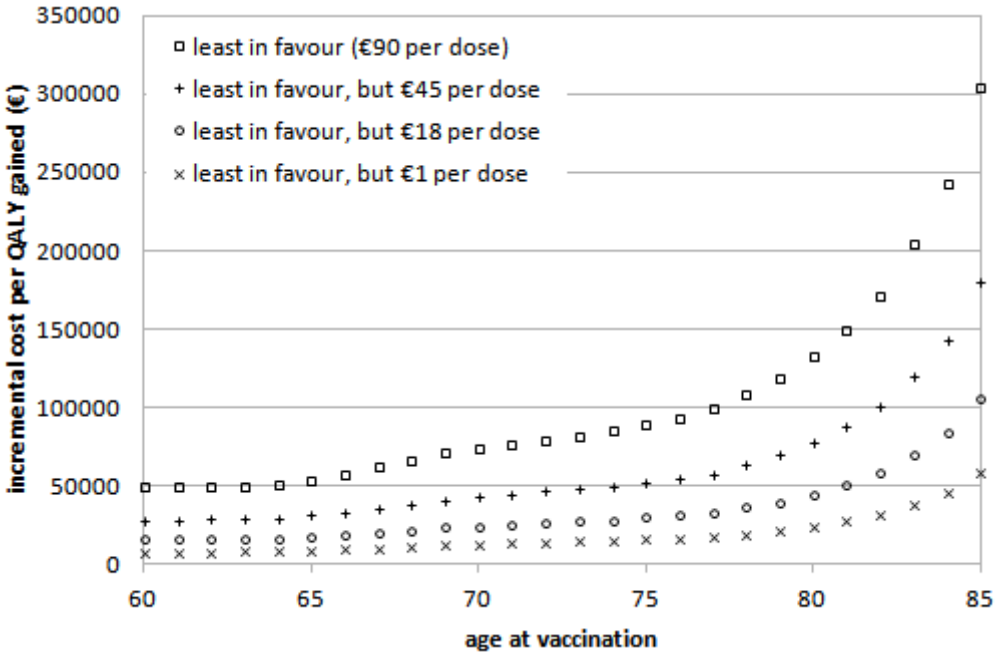
4.1.2.5 *Vaccine price.*

For the incremental cost to be below €30000 per QALY gained in the scenario least in favour of vaccination, the vaccine price per dose should drop as follows, for each of the following targeted age cohorts (Figure 44):

- Age cohorts 60-75: €18
- Age cohorts 60-64: €45

Note that these prices are markedly lower than what the cost-effectiveness analyses produced by the vaccine manufacturer have predicted to be cost-effective (e.g. Annemans et al[92] for such an analysis applied to Belgium).

Figure 44: Incremental cost per Quality-Adjusted Life-Year (QALY) gained of vaccinating against HZ compared to not vaccinating, for age cohorts 60 up to 85. Results of a univariate scenario analysis based on the scenario least in favour of vaccination: scenarios are shown for different prices of the vaccine.



4.1.2.6 *Vaccine coverage.*

Under the static cohort model approach of the economic evaluation of HZ vaccination, and given that there are no costs that scale nonlinearly to vaccination coverage, the cost per QALY gained remains constant under any variation of vaccination coverage. For a formal elaboration of this phenomenon, see Beutels[93]. Therefore, the budget-impact is of greater interest to estimate under various levels of vaccination uptake.

Figure 45: Incremental cost of vaccinating against HZ compared to not vaccinating, for age cohorts 60 up to 85. Results are shown for the scenario most in favour of vaccination, but with the vaccine coverage altered.

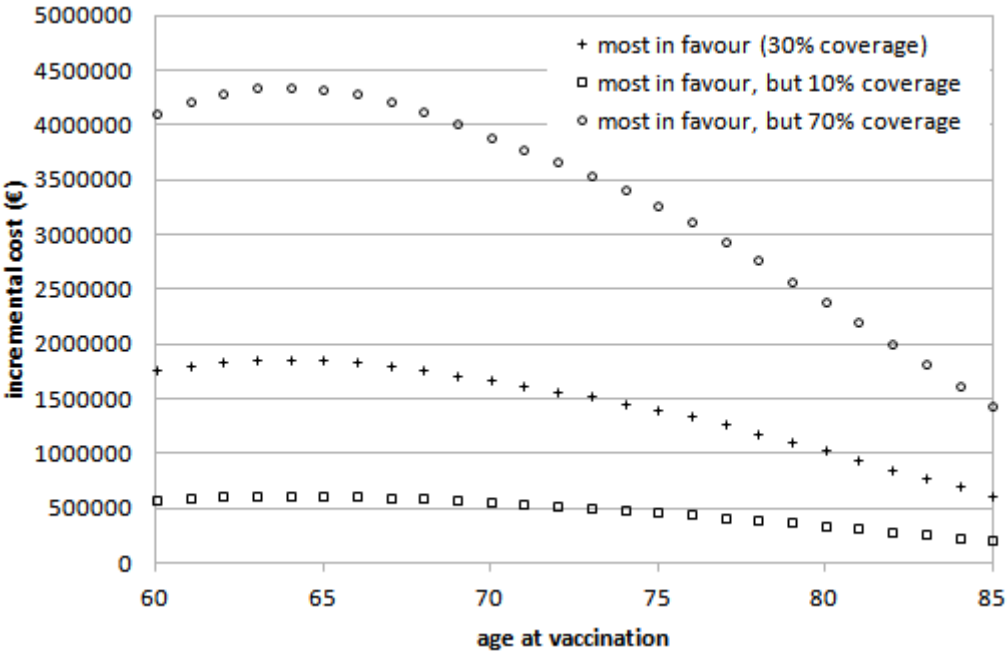


Figure 48 shows that – given 30% uptake of the vaccine (which would be similar to the uptake of other vaccines in this age group in Belgium) – roughly between €0.6 million and €1.8 million per targeted age cohort is incurred in net direct costs to the health system. So targeting everyone between 60 and 70 years of age and achieving 30% uptake in this age group would amount to net costs of about €20 million the first year, and €1.8 million per year thereafter. Note that there is a direct relation between coverage and the net costs, implying a doubling of uptake implies a doubling of the net costs.

4.2 PRIMARY VZV (CP) VACCINATION: RESULTS

The HZ-related parameters used as input in the model, are the ones described above for the scenario least in favour of vaccination, except for:

- Assuming that all HZ episodes (i.e. not only HZ episodes in immunocompetent persons) can be prevented by HZ vaccination.
- Using the estimate for waning of HZ vaccine efficacy obtained by van Hoek et al[43]. This means that the vaccine protects on average for about 7.5 years, and that waning occurs according to an exponential function.

Two sets of scenarios are run:

1) Vaccination scenarios assuming exogenous boosting (i.e. parameters k and z of the dynamic model set to 100%).
2) Vaccination scenarios assuming no exogenous boosting (i.e. parameter k and z of the dynamic model set to 0).

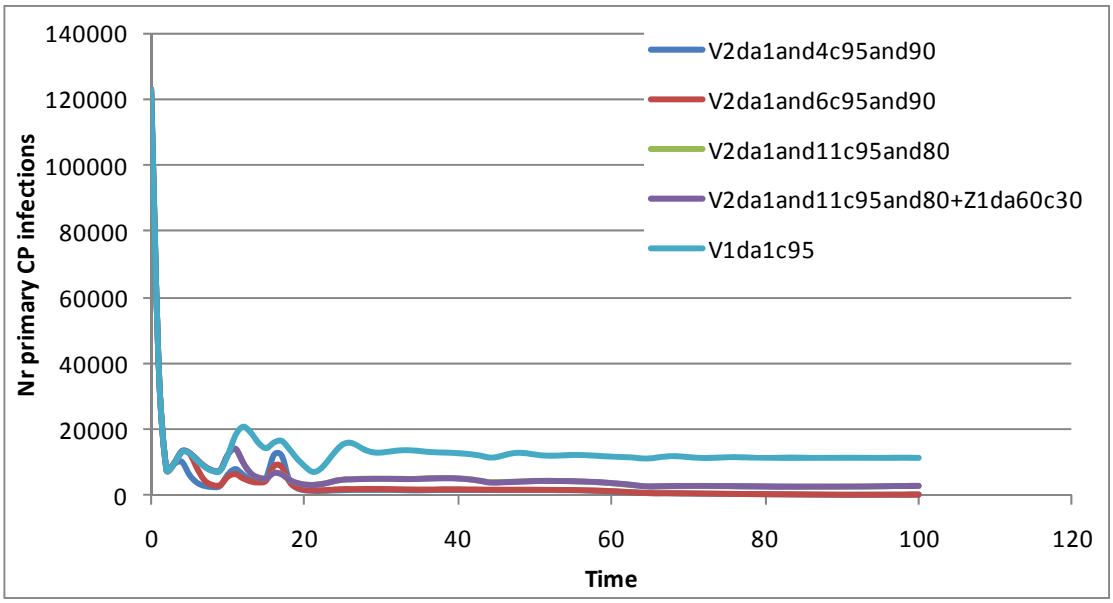
4.2.1 Impact of vaccination against CP (and HZ) assuming exogenous boosting

4.2.1.1 Impact of vaccination on annual number of CP and HZ infections

Figure 46 through Figure 48 show the impact of five different vaccination scenario's on the annual number of primary and breakthrough CP infections and HZ infections over time in Belgium, using coverage rates derived from other vaccination programmes at the same or similar ages in Belgium.

Figure 46 shows that – as could be expected – the incidence of CP declines dramatically and rapidly after the introduction of childhood vaccination in Belgium. After some initial fluctuations the infection settles around an equilibrium state. Clearly the decision to have a second dose has a larger impact than the timing of that second dose. It is shown below that a second dose at age 11 years offers the most cost-effective timing for the second dose in the Belgian context, but that the differences in (cost-)effectiveness between the second dose at ages 4, 6 or 11 years remain small.

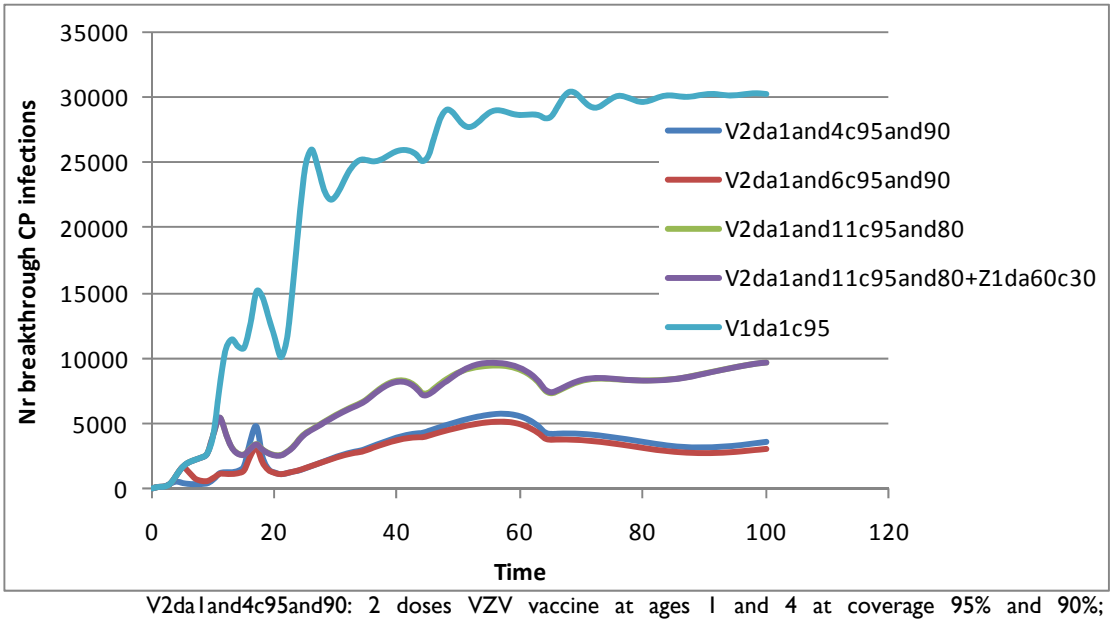
Figure 46: Number of primary CP infections over time for 5 different vaccination scenario's. Time point 0 represents the situation without vaccination. Note that the green line is completely covered by the purple line.



V2da1and4c95and90: 2 doses of VZV vaccine at ages 1 and 4 at coverage 95% and 90%; V2da1and6c95and90: 2 doses of VZV vaccine at ages 1 and 6 at coverage 95% and 90%; V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Z1da60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Figure 47 shows that single dose VZV vaccination gives rise to considerably more breakthrough infections than two-dose VZV vaccination, and that the longer one waits before administering the second dose, the more primary vaccine failures (or breakthrough infections) will occur.

Figure 47: Number of breakthrough CP infections over time for 5 different vaccination scenario's. Time point 0 represents the situation without vaccination. Note that the green line is completely covered by the purple line.

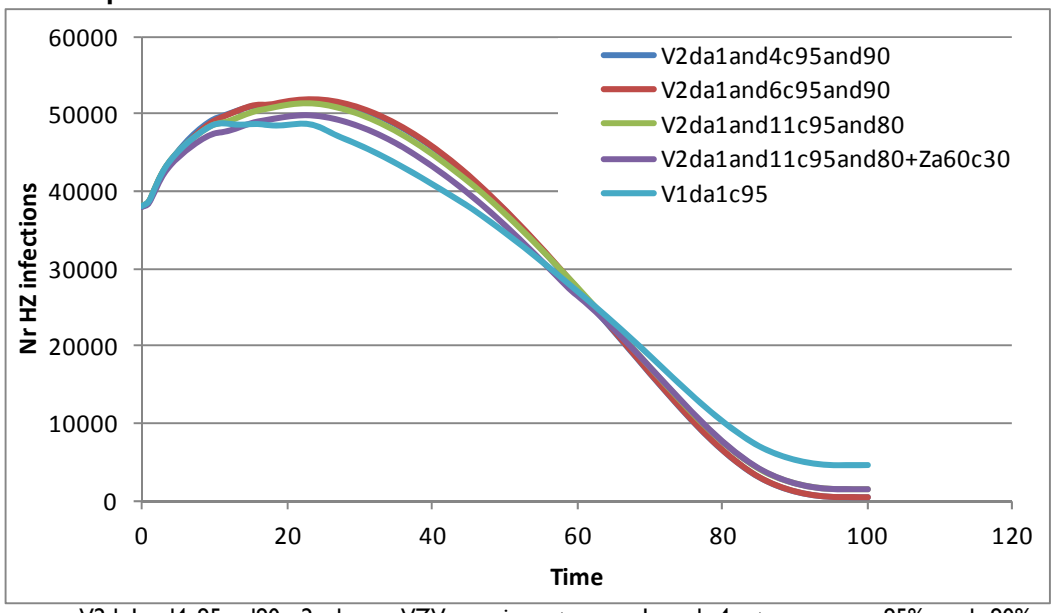


V2da1and4c95and90: 2 doses VZV vaccine at ages 1 and 4 at coverage 95% and 90%; V2da1and6c95and90: 2 doses VZV vaccine at ages 1 and 6 at coverage 95% and 90%;

V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Z1da60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Figure 48 shows that each of the VZV vaccination strategies results in a temporary increase in HZ infections (due to the exogenous boosting mechanism), which would last for about 40-50 years.

Figure 48: Number of HZ infections (in unvaccinated people, i.e. 'Zoster' in Figure 33) over time for 5 different vaccination scenarios. Time point 0 represents the situation without vaccination.



V2da1and4c95and90: 2 doses VZV vaccine at ages 1 and 4 at coverage 95% and 90%; V2da1and6c95and90: 2 doses VZV vaccine at ages 1 and 6 at coverage 95% and 90%; V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Za60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Figure 49 through Figure 56 illustrate the impact of different vaccination scenario's on the age-specific annual number of primary and breakthrough CP infections and HZ infections.

Figure 49 and Figure 50 show that after an initial "mop-up" in 5-9 year olds, the residual cases of primary CP would mainly occur amongst 15-24 year olds, about 10 to 20 years after the start of the programme. From then on, the residual caseload would be quite low at less than 2000 cases per year, and appear mostly in 25-59 year olds.

Figure 49: Scenario CP 2-dose vaccination at ages 1 and 4 years, at coverage 95% and 90%: Number of primary CP infections over time, by age group. Time point 0 represents the situation without vaccination.

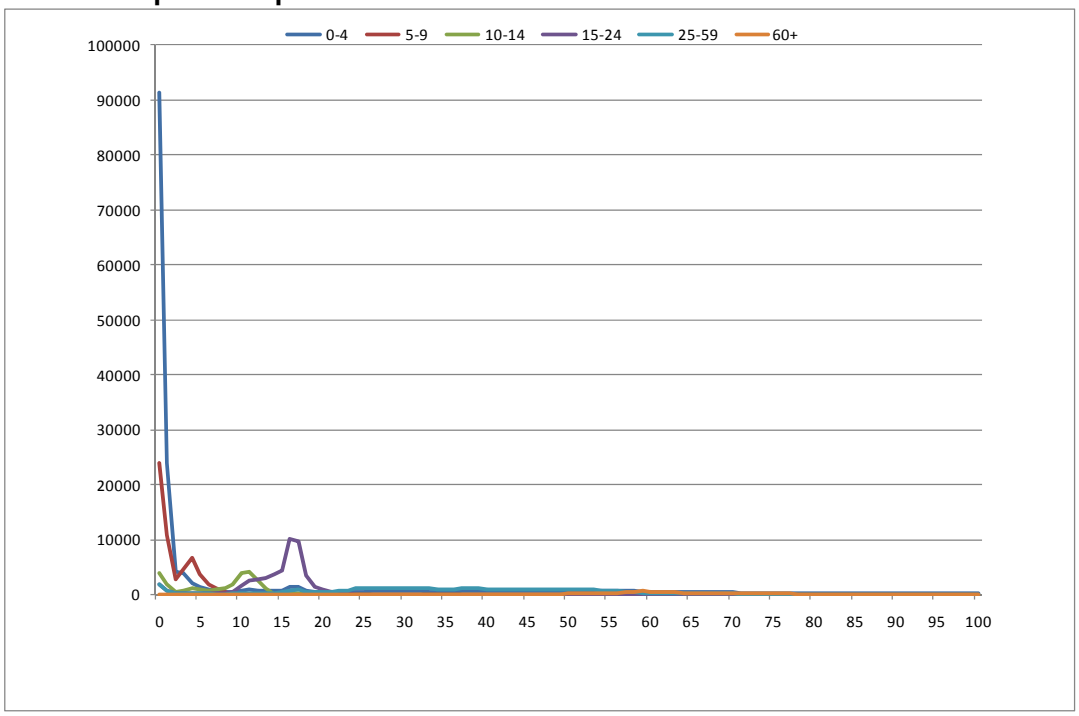


Figure 50: Scenario CP 2-dose vaccination at ages 1 and 4 years at coverage 95% and 90%: Identical to Figure 49, but X-axis starts from time point 2.

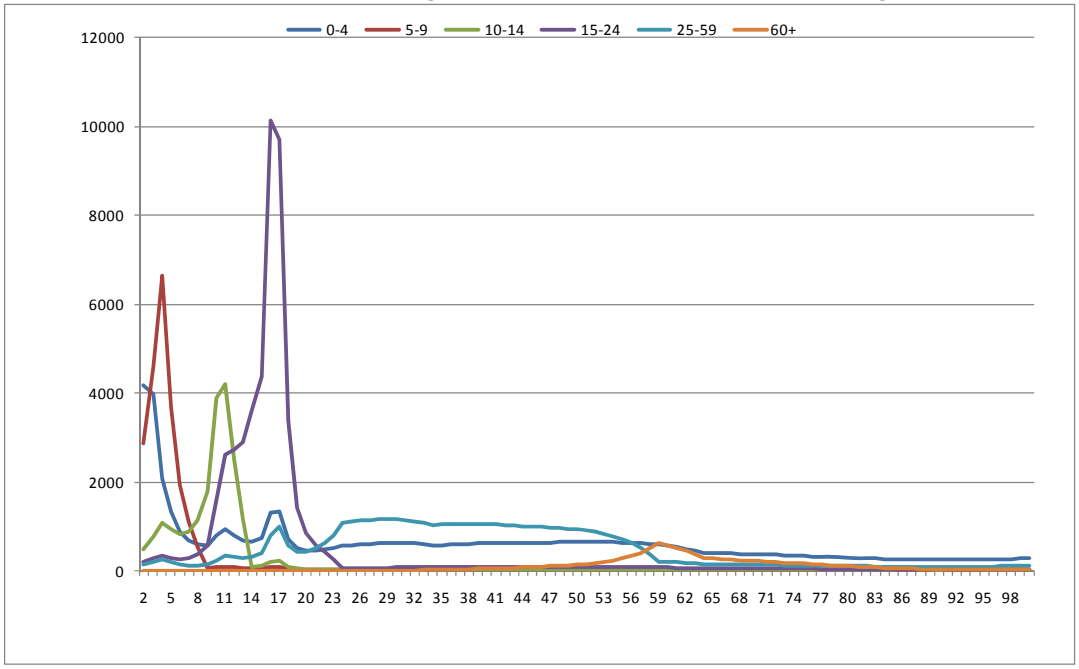


Figure 51 and Figure 52 show that the increase in HZ following CP vaccination is predicted to occur mainly in adults, since they are at greater risk of HZ prior to vaccination. The increase is more pronounced in adults under 60 years of age, with a doubling in caseload after 25 years of childhood CP vaccination (Figure 51). For older adults the relative increase is less pronounced, but the nominal increase in cases is larger, due to the higher caseload to start with (Figure 51).

Figure 51: Scenario CP 2-dose vaccination at age 1 and 11 years at coverage 95% and 80%: Number of HZ infections (in unvaccinated people, i.e. 'Zoster' in Figure 33) over time, by age group.

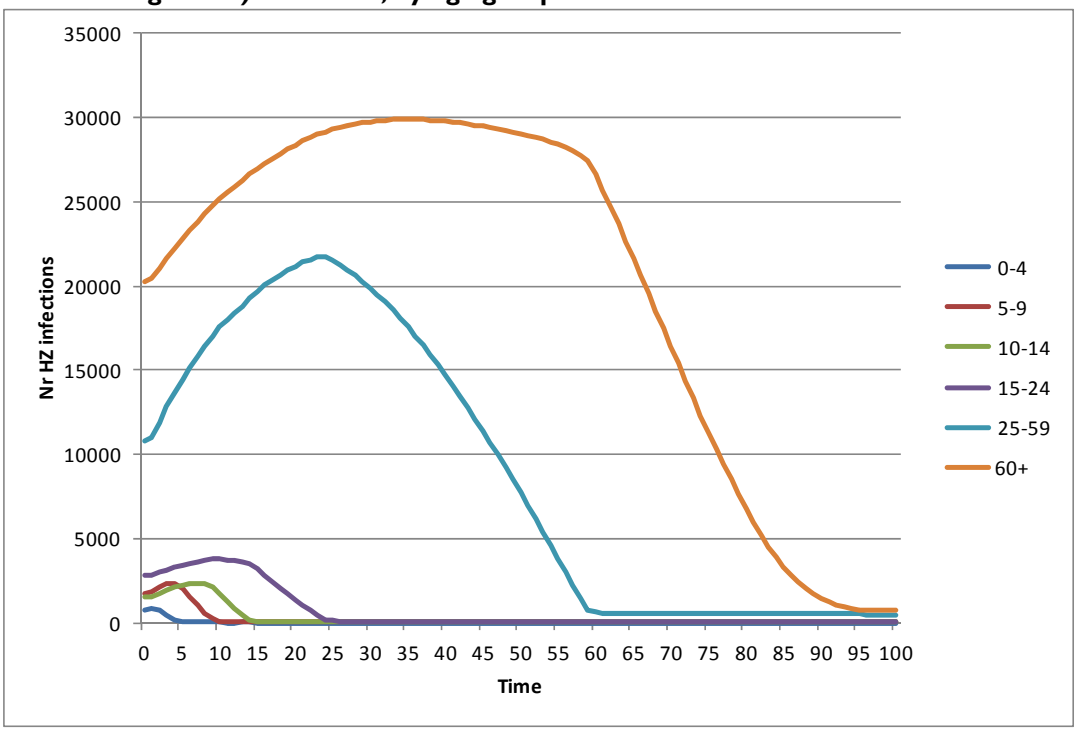
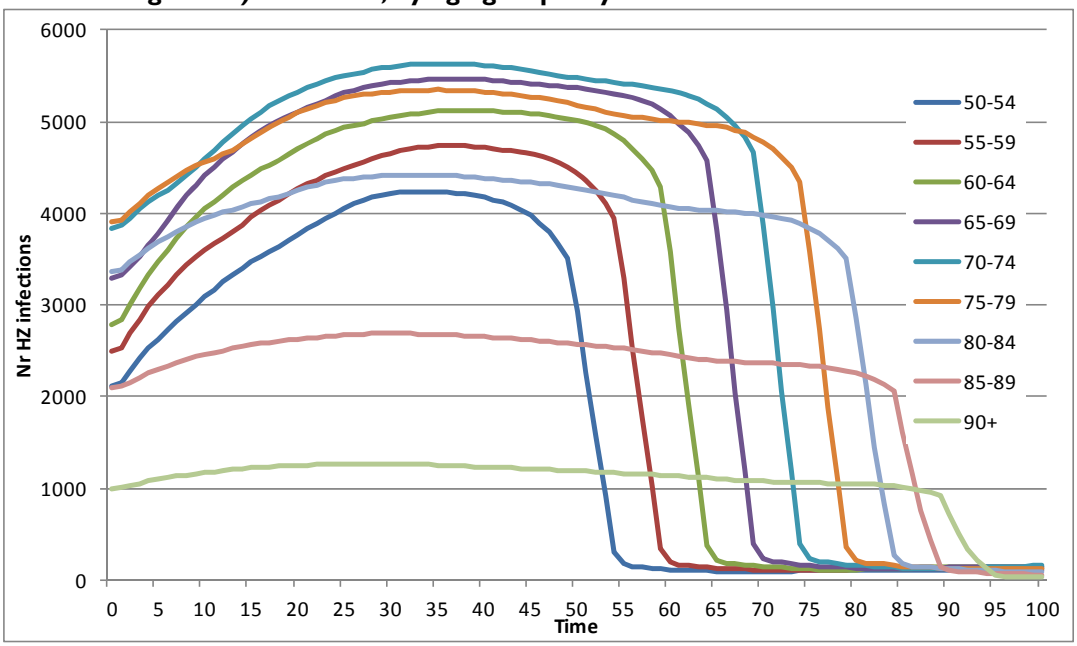
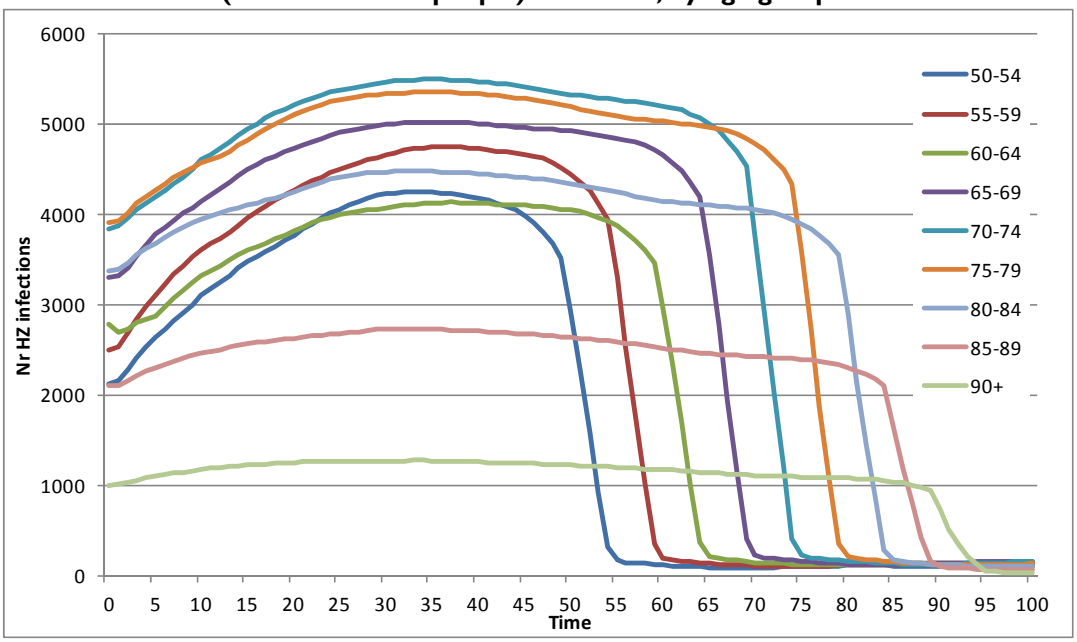


Figure 52: Scenario CP 2-dose vaccination at age 1 and 11 years, at coverage 95% and 80%: Number of HZ infections (in unvaccinated people, i.e. 'Zoster' in Figure 33) over time, by age group 50 years and older.



The comparison of Figure 53 with Figure 52 indicates that the role of HZ vaccine to amend the problem created by CP vaccination is limited, particularly at our baseline uptake rate of 30%, based on similar vaccination programmes in that age group.

Figure 53: Scenario CP 2-dose vaccination at age 1 and 11 years at coverage 95% and 80% + HZ booster at age 60 at 30% coverage: Number of HZ infections (in unvaccinated people) over time, by age group.



Although the Belgian Superior Health Council no longer wishes to consider single dose vaccination options in Belgium, in view of the expected high number of CP cases in vaccinees (based on the experience in the USA), we show in Figure 54 through Figure 56 for the purpose of illustration what can be expected under such a strategy.

Figure 54: Scenario CP 1-dose vaccination at age 1 year at 95% coverage: Number of primary CP infections over time, by age group. Time point 0 represents the situation without vaccination.

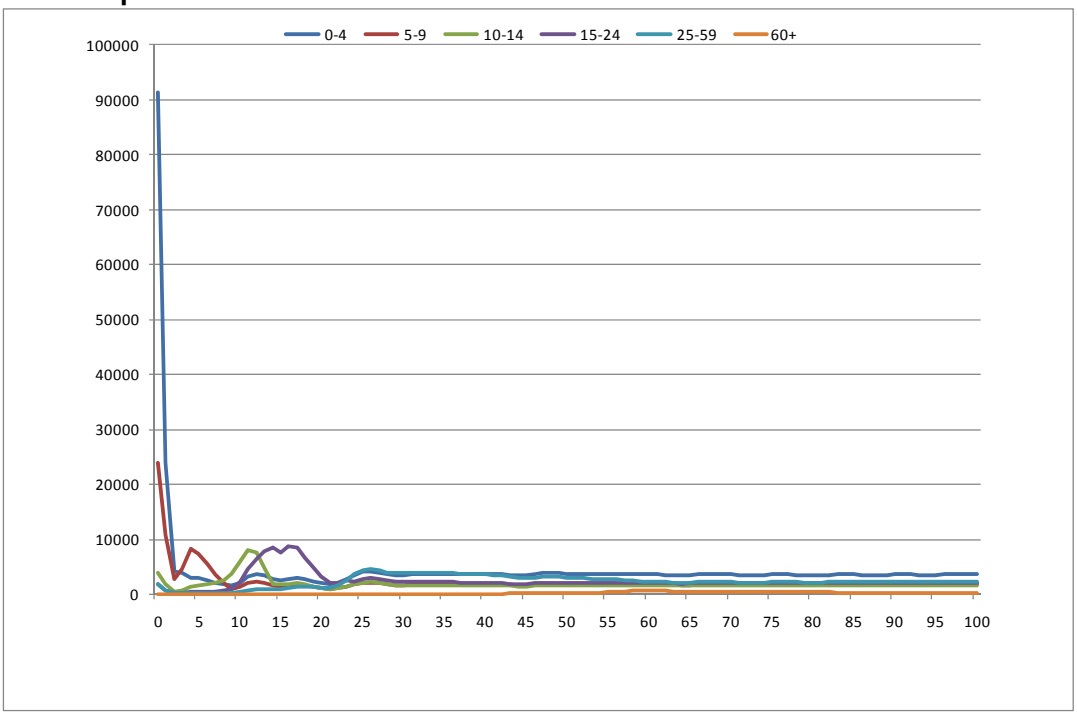


Figure 55: Scenario CP 1-dose vaccination at age 1 year at 95% coverage: Identical to Figure 54 but X-axis starts from time point 2.

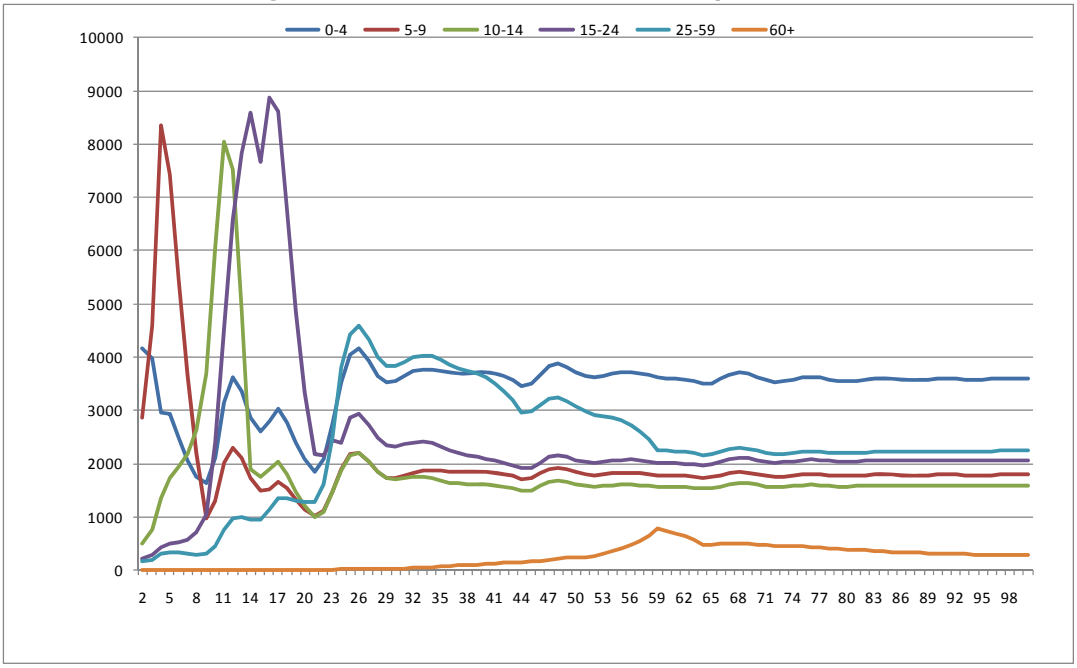
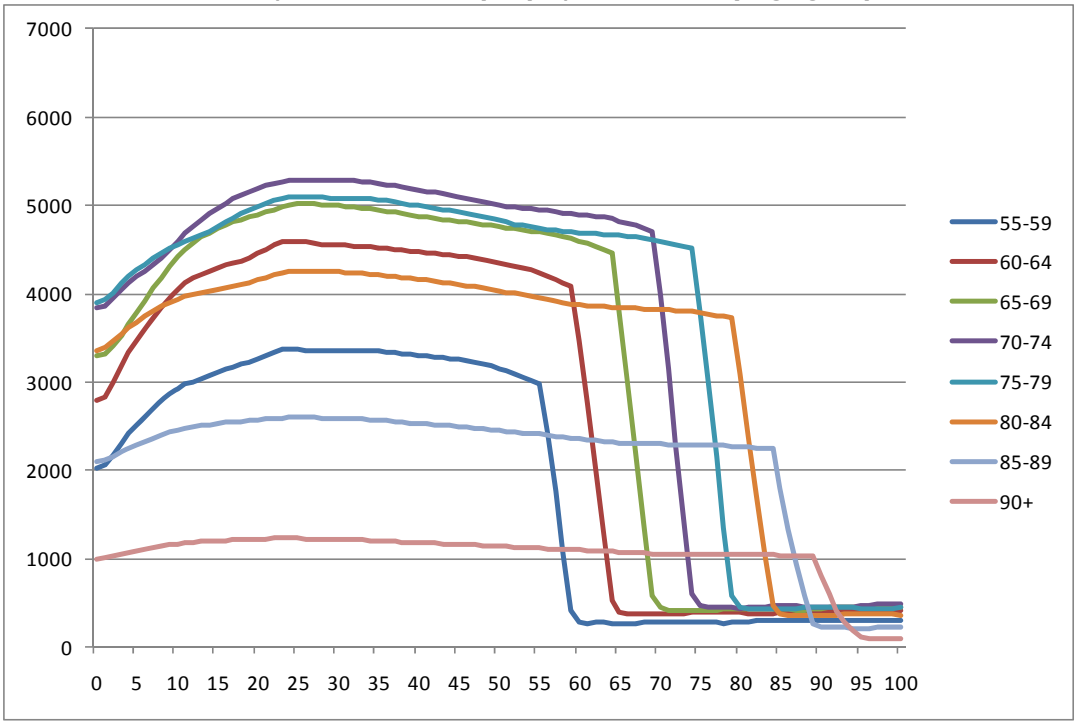


Figure 54 and Figure 55 show – as expected – that the residual caseload after 20 years is still markedly higher in multiple age groups compared to two-dose CP vaccination. At the same time, the increase in HZ incidence is less pronounced (Figure 56).

Figure 56: Scenario CP 1-dose vaccination at 1 at 95% coverage: Number of HZ infections (in unvaccinated people) over time, by age group.



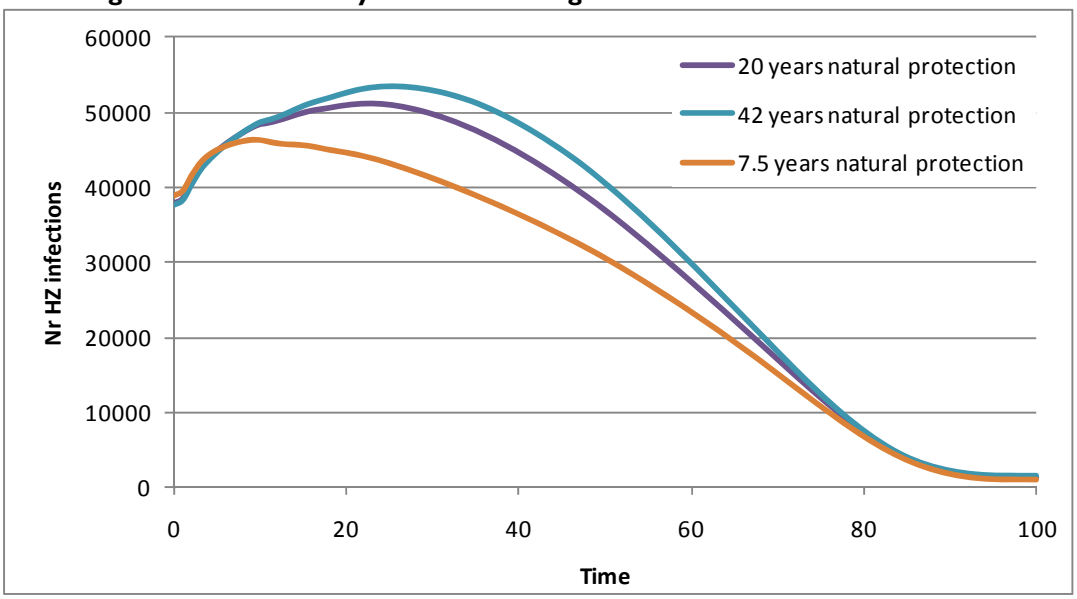
From the incidence plots of the above selection of childhood VZV vaccination options, it is clear that:

1. For all vaccination scenarios considered, a universal CP vaccination program results in an increase in HZ infections the first 40-50 years after its introduction (Figure 48).
2. Additional boosting with HZ vaccine at age 60 years (at 30% coverage) to prevent HZ, has only a very small effect in altering this increase in HZ infections (Figure 53 compared to Figure 52).
3. A vaccination program with only one dose of CP vaccine compared to two doses of the vaccine, results in a smaller decrease in primary CP infections, a higher number of breakthrough CP infections, but a lower increase in HZ infections the first 40-50 years after the introduction of the vaccination program (Figure 46, Figure 47 and Figure 48).
4. The predicted increase in HZ infections due to the introduction of a CP vaccination program is predicted to occur mainly in adults. The relative increase is more pronounced in adults under 60 years of age (Figure 51), but the nominal increase in cases is larger in older adults, due to the higher caseload to start with (Figure 51).
5. A CP vaccination program decreases substantially the number of CP infections in children younger than 10 years of age, but results in a (temporary) increase in cases of age 10 and older (Figure 49, Figure 50, Figure 54 and Figure 55).

How sensitive are these results to some key input parameters of the dynamic model?

- Duration of protection against HZ induced by natural boosting: the shorter the assumed duration of protection through natural boosting, the smaller the initial increase in HZ infections (Figure 57). The number of HZ infections about 80 years after the introduction of CP vaccine is independent of the assumption on the duration of protection from natural boosting (Figure 57).
- CP vaccine effectiveness: the shorter the duration of CP vaccine effectiveness, the smaller the initial increase in HZ infections, but the higher the number of HZ infections over a long time period, and the lower the decrease in CP infections (results not shown).
- HZ vaccine efficacy: This has only an effect on the scenarios including HZ booster vaccination. The longer HZ vaccine efficacy lasts, the lower the number of HZ infections (results not shown).
- HZ reactivation rate in CP vaccinees (parameter 'χ'): this has only effect on the HZ infections in patients vaccinated against CP. The lower χ, the more CP vaccination results also in a decrease of the annual number of HZ infections in the long run (results not shown).
- Age-specific disease transmission matrix: We did not integrate the impact of uncertainty regarding the choice of age-specific mixing patterns as part of the current analysis. However, in separate statistical and mathematical modelling studies, Ogunjimi et al[31] and Goeyvaerts et al[90] have shown (using different methods) that with social contacts which involve touching and with an accumulated contact time of more than 15 minutes per contact-day, better fits can be obtained to seroprevalence data (amongst a range of countries, including Belgium) than using previous standard approaches (using simplified mixing matrices as proposed in Anderson & May[94]) or other definitions of contact data collected in large country-specific surveys[29, 30]. Van Effelterre et al[32] showed that the choice of matrix (amongst the Anderson & May[94] configurations) can be very influential for dynamic models of VZV transmission, and this aspect has not been explored in any dynamic model based economic evaluation predating 2010. We believe we have used the best social mixing dataset available for our analysis based on the work of Ogunjimi et al[31] and Goeyvaerts et al[90].

Figure 57: Scenario CP 2-dose vaccination at 1 and 11 at coverage 95% and 80%: Number of HZ infections (in unvaccinated people, i.e. 'Zoster' in Figure 33) over time, for 3 different assumptions on the duration of protection against HZ induced by natural boosting.

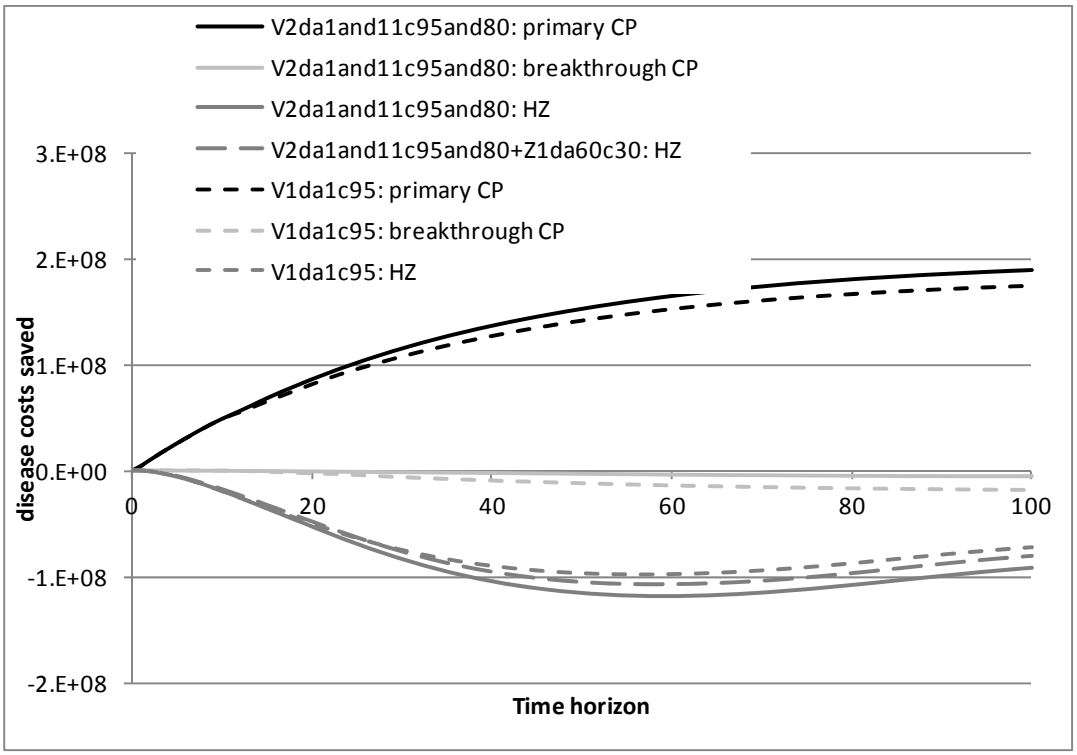


4.2.1.2 Impact of vaccination on CP and HZ-related costs and consequences

Figure 58, Figure 59 and Figure 60 show how the introduction of a CP (and HZ) vaccination program in Belgium, results in accumulated disease costs saved or lost, life years gained or lost, QALY's gained or lost, depending on the time horizon taken into account. We can see that:

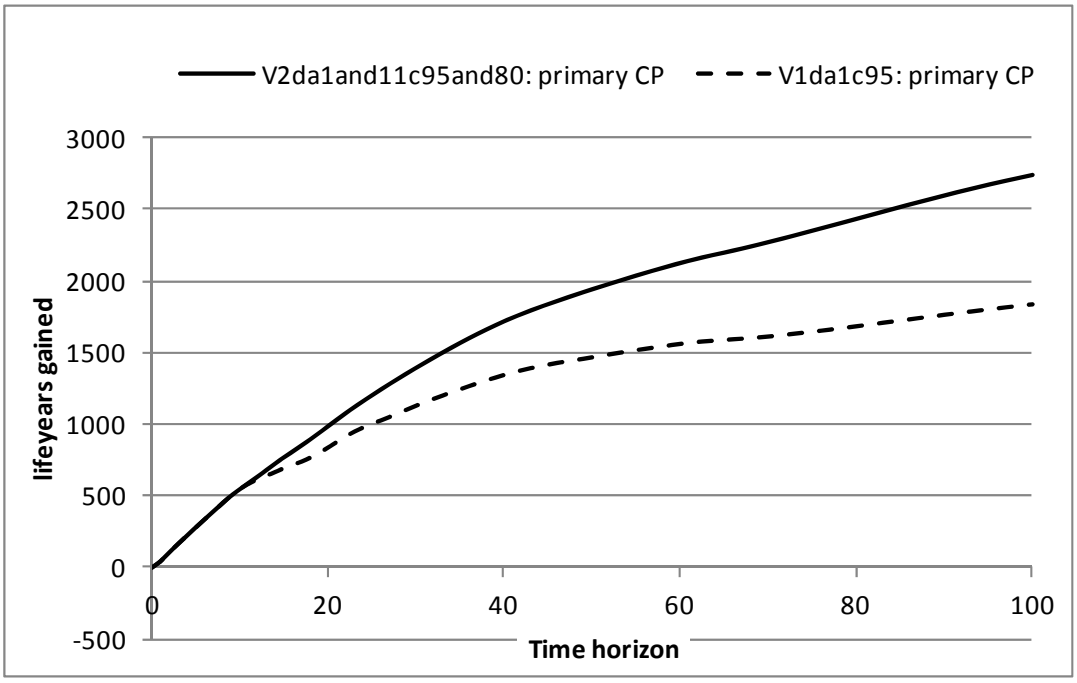
1. The accumulated disease costs and life years lost for a certain time horizon, related to the occurrence of breakthrough CP infections and the increase in HZ infections when introducing CP vaccine, is more than compensated by accumulated costs saved and life years gained because of the prevention of primary CP infection (Figure 58 and Figure 59).
2. For time horizon of about 10 until 80 years after vaccination, the vaccination programme is predicted to lead to an overall loss in QALYs in the population. Only after that time (about 80 years after vaccination), the accumulated QALY's gained through preventing primary CP infections when introducing a CP vaccination program, make up for the QALY's lost because of extra HZ infections after the introduction of the CP vaccine (Figure 60).
3. The burden related to breakthrough CP is subordinate to the HZ-related burden.

Figure 58: Primary and breakthrough CP and HZ-related accumulated disease costs saved/lost according to time horizon taken into account, for 3 different vaccination scenario's. Costs are discounted at 3%.



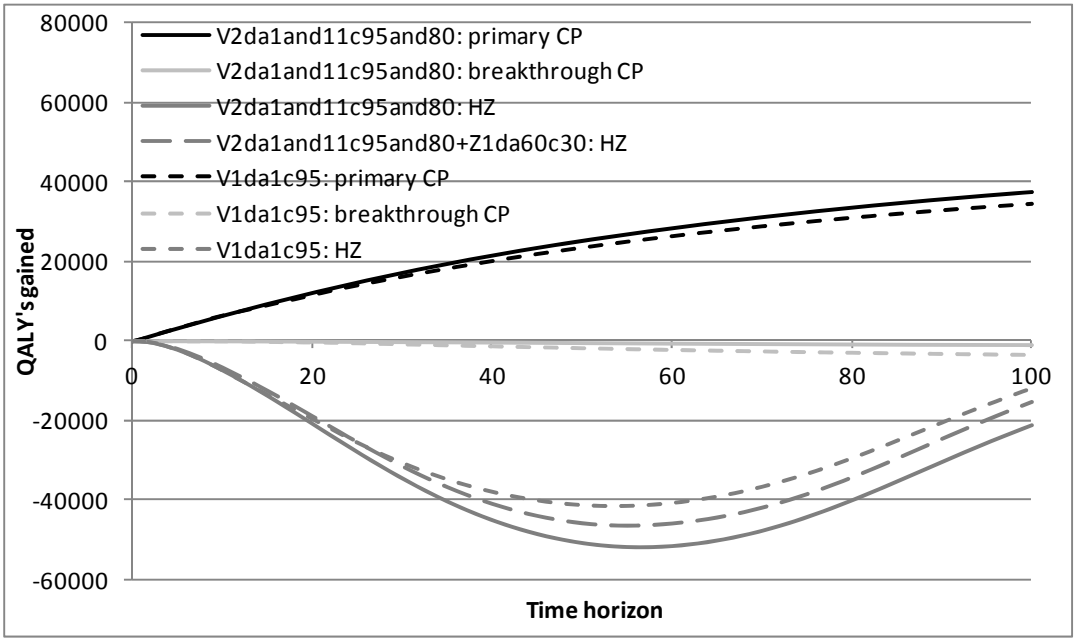
V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Z1da60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Figure 59: Primary and breakthrough CP and HZ-related accumulated life years gained/lost according to time horizon taken into account, for 2 different vaccination scenario's. Life years are discounted at 1.5%. No lifeyears are gained for breakthrough CP and HZ, because no breakthrough CP and HZ-related deaths were assumed.



V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Figure 60: Primary and breakthrough CP and HZ-related accumulated QALY's gained/lost according to time horizon taken into account, for 3 different vaccination scenario's. QALY's are discounted at 1.5%.



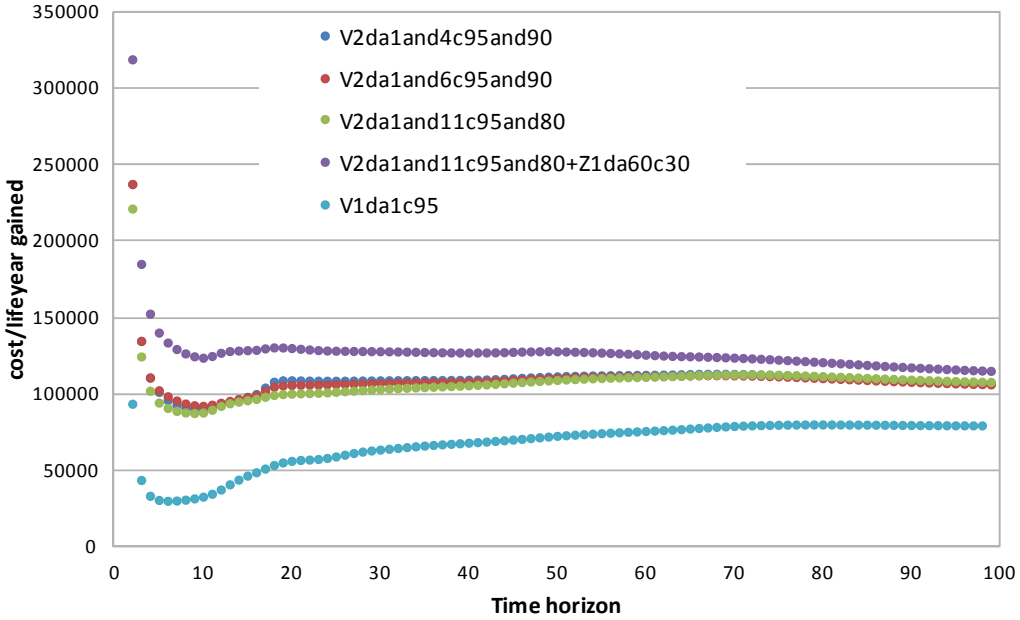
V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Z1da60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Hence, a key observation is that CP vaccination would entail an overall QALY loss. This observation is sensitive to how high/low the value of CP-related QALY loss is estimated/assumed compared to the HZ-related QALY loss. Note that we estimated relatively high disutility weights for CP compared to other studies[48, 50] and that we used relatively low disutility weights for HZ (based on the SOIS obtained from Scott et al[34]). Therefore, the overall result that CP vaccination would entail an overall QALY loss would not change if we were to use alternative estimates from studies in other countries. However, we can investigate the impact of taking into account QALY loss for one caregiver of a person with CP (assuming it to be the same as for a person with rotavirus disease[52]). Taking into account QALY loss for a caregiver of a person suffering from CP does not change the finding that for several decades after the introduction of CP vaccination, a net loss in QoL is expected (Figure 63).

4.2.1.3 Cost per life year gained and cost-utility of CP (and HZ) vaccination

Figure 61 shows the incremental direct cost per life year gained for five possible CP and HZ vaccination scenario's compared to no vaccination, as a function of the time horizon. It seems clear that two-dose CP vaccination remains above €85,000 per life-year gained, and that single dose CP vaccination remains above €30,000 per life-year gained.

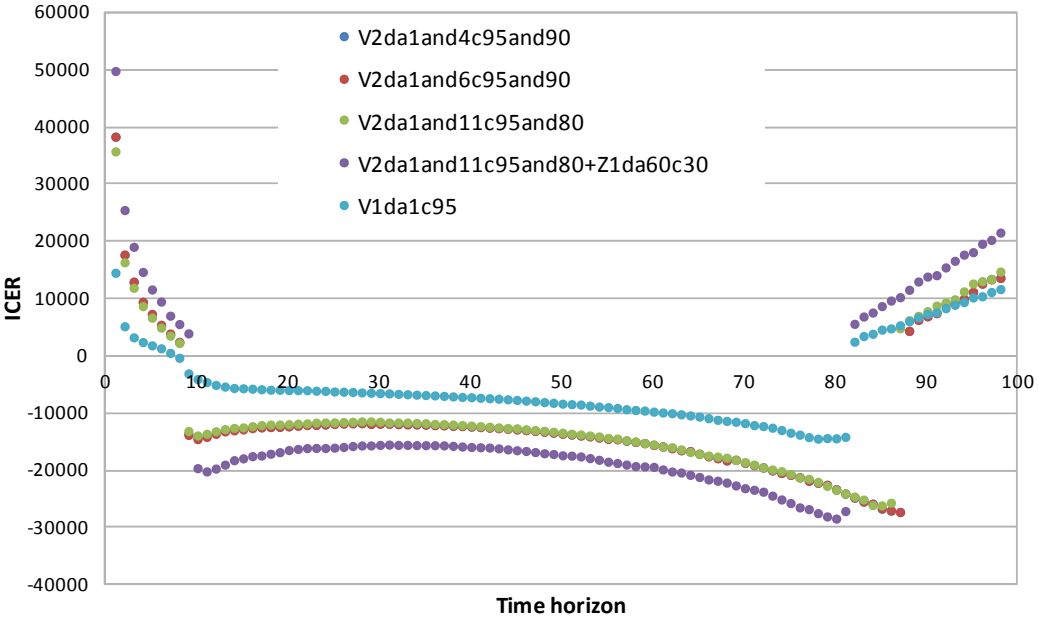
Figure 61: Incremental direct cost per life-year gained for 5 different CP (and HZ) vaccination scenario's in Belgium, compared to no vaccination, over time. Discount rate for costs 3%, for life years 1.5%.



V2da1and4c95and90: 2 doses VZV vaccine at ages 1 and 4 at coverage 95% and 90%; V2da1and6c95and90: 2 doses VZV vaccine at ages 1 and 6 at coverage 95% and 90%; V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Z1da60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

Figure 62 shows the incremental direct cost per QALY gained of these scenario's compared to no vaccination.

Figure 62: Incremental direct costs per QALY gained ('ICER', €) for 5 different CP (and HZ) vaccination scenarios in Belgium, compared to no vaccination, over time. Discount rate for costs 3%, for effects 1.5%. Negative ICER's are caused by QALY losses for vaccination versus no vaccination.



V2da1and4c95and90: 2 doses VZV vaccine at ages 1 and 4 at coverage 95% and 90%; V2da1and6c95and90: 2 doses VZV vaccine at ages 1 and 6 at coverage 95% and 90%;

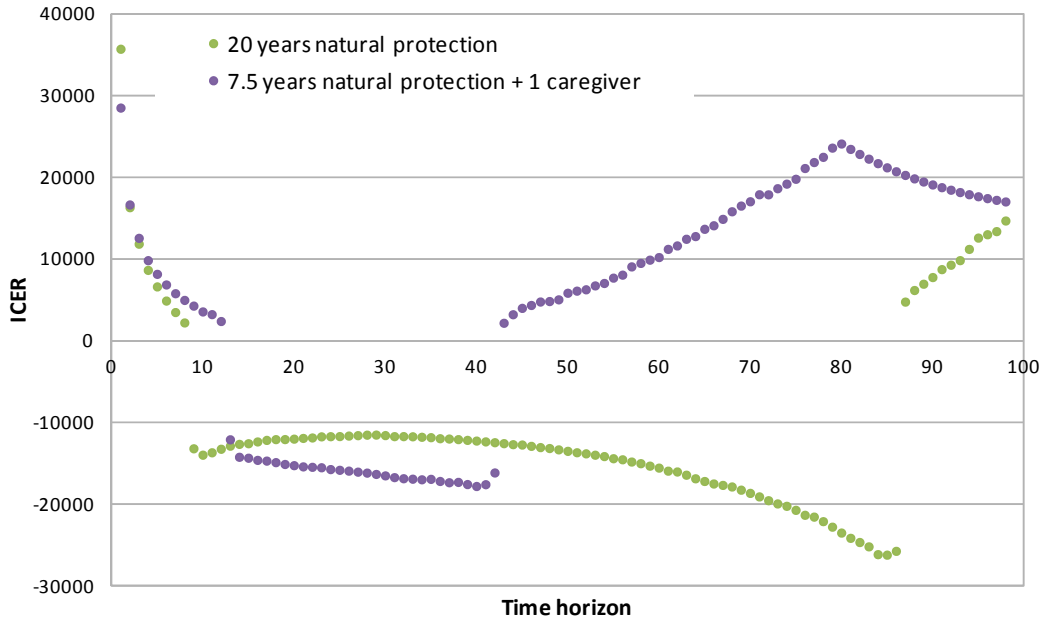
V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Z1da60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage

From Figure 62 it is clear that:

1. The cost-effectiveness of CP (with additional HZ) vaccination is highly dependent on the time horizon considered, and consequently on the discount rates for costs and effects.
2. A program with only a single dose of the VZV vaccine is more cost-effective than a 2-dose strategy for a very short or long time horizon, mainly because it results in smaller HZ-related QALY losses compared to a 2-dose strategy, whereas its CP-related QALY gain is not that much smaller.
3. A two-dose VZV vaccine is not cost-effective compared to not vaccinating for many decades, even if giving an additional booster in adults to prevent HZ. The scenario considering a HZ booster, involves the extra cost of this booster vaccine for only a small reduction in HZ-related QALY loss compared to 2-dose strategy.

Figure 63 shows that, even with the assumption of a short duration of protection from natural boosting (7.5 years, lowest end of the 95% CI obtained by Brisson et al[71]), and taken into account QALY loss for a caregiver of a person suffering from CP (assumed to be the same as estimated for a person with RV[52]), does not change the finding that for several decades after the introduction of CP vaccination, a net loss in QoL is expected.

Figure 63: Incremental direct costs per QALY gained ('ICER', €) for a 2-dose CP vaccination scenarios at age 1 and 11 and coverage 95% and 80% in Belgium, compared to no vaccination, over time. Discount rate for costs 3%, for effects 1.5%. Negative ICER's are caused by QALY losses for vaccination versus no vaccination.



4.2.1.4 Impact of spurious vaccination (vaccine uptake levels of 50%)

At vaccine uptake levels of 50%/50% compared with 95%/80% as in a program, the total annual number of cases of chickenpox in adults (age 25 and older) will be higher than the situation without vaccination (Figure 64). Compared with uptake levels of 95/80%, at vaccine uptake levels of 50%/50%, the increase in HZ cases for the first 35 years will be substantially lower (Figure 65), but still, up to 70 years after vaccination, a net loss in QALY's is expected (Figure 66).

Figure 64: Scenario CP 2-dose vaccination at age 1 and 4 at 95/90% coverage compared to 50/50% coverage: Number of primary CP infections over time, by age group. Time point 0 represents the situation without vaccination. Only age groups 10 and older are shown.

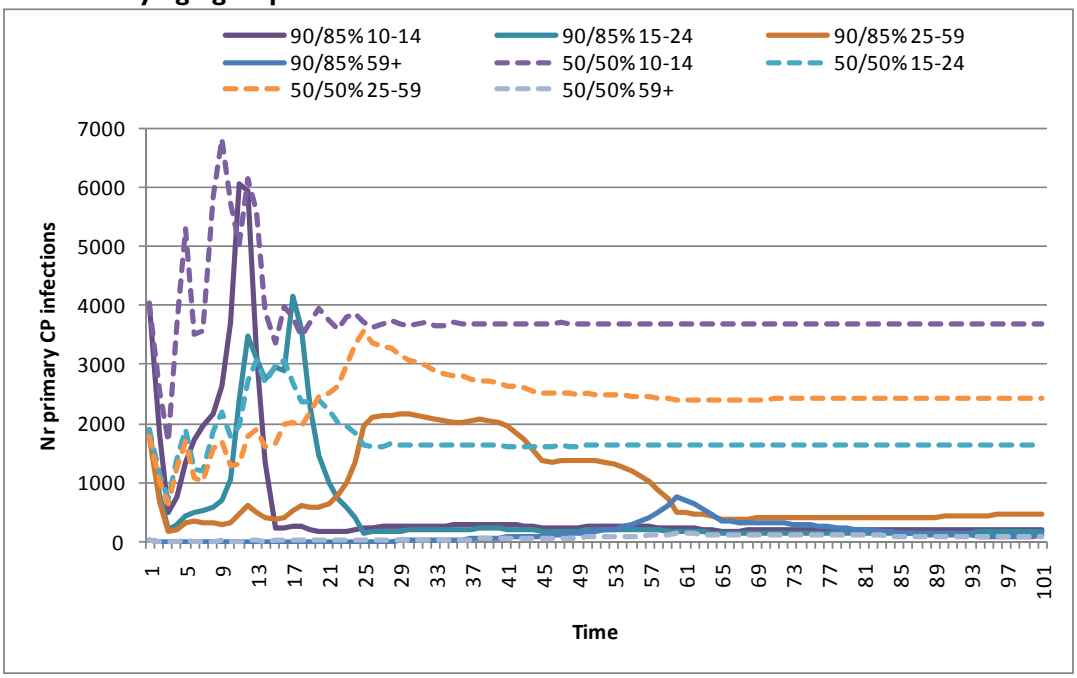
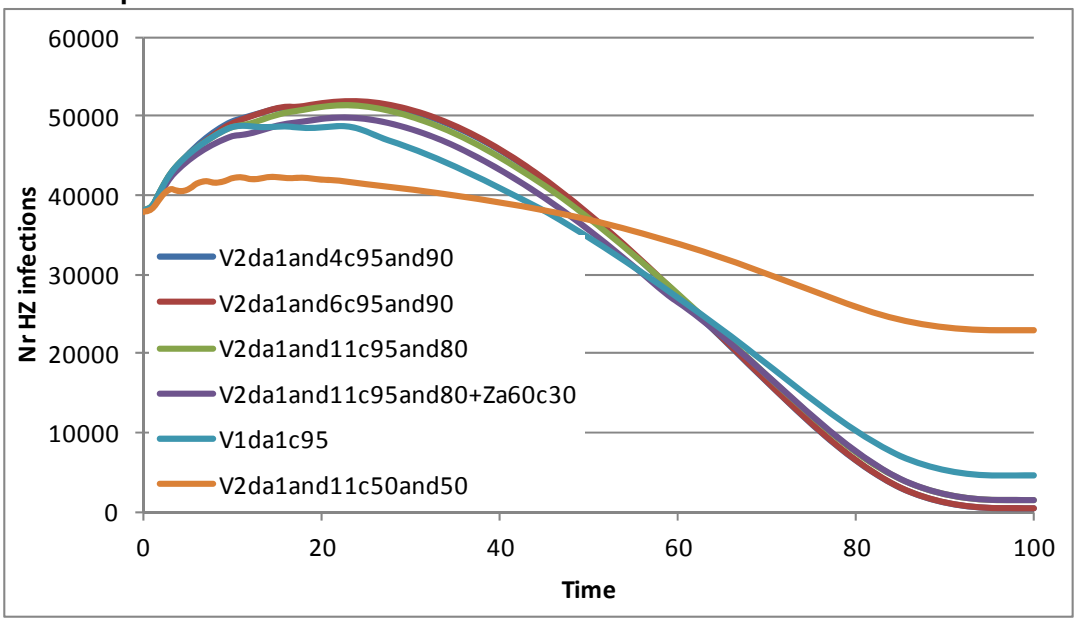


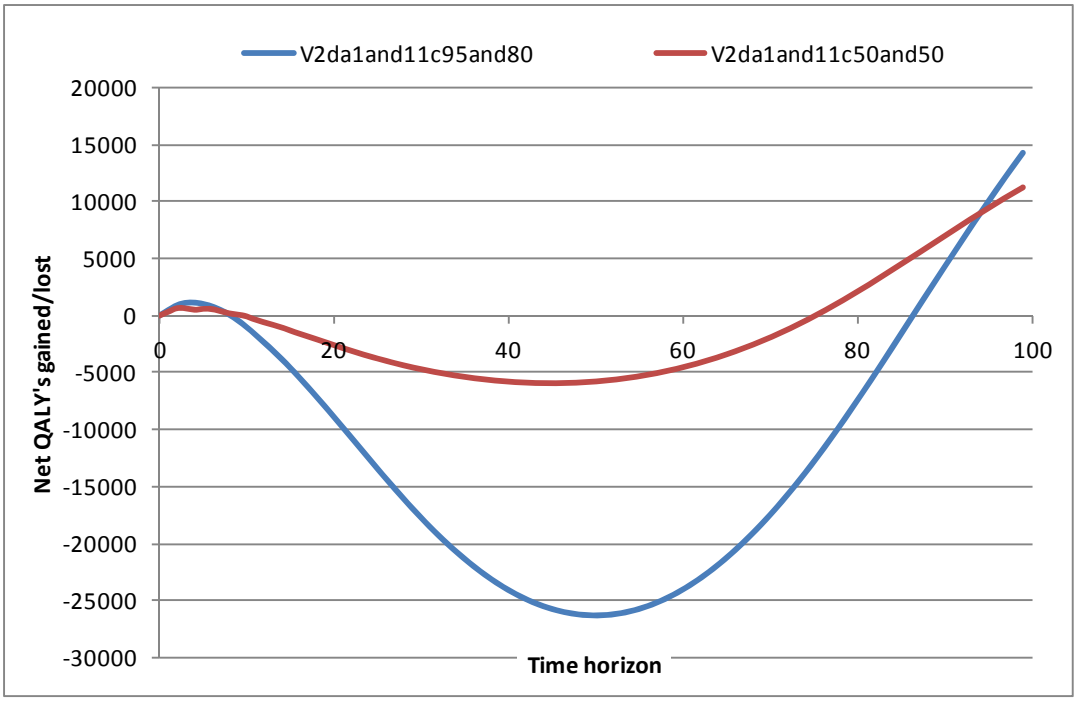
Figure 65: Number of HZ infections (in unvaccinated people, i.e. 'Zoster' in Figure 33) over time for 6 different vaccination scenario's. Time point 0 represents the situation without vaccination.



V2da1and4c95and90: 2 doses VZV vaccine at ages 1 and 4 at coverage 95% and 90%;
V2da1and6c95and90: 2 doses VZV vaccine at ages 1 and 6 at coverage 95% and 90%;

V2da1and11c95and80: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80%; V2da1and11c95and80+Za60c30: 2 doses VZV vaccine at ages 1 and 11 at coverage 95% and 80% + 1 dose of HZ vaccine at age 60 at 30% coverage; V1da1c95: 1 dose VZV vaccine at ages 1 at 95% coverage; V2da1and11c50and50: 2 doses VZV vaccine at ages 1 and 11 at coverage 50% and 50%

Figure 66: Scenario CP 2-dose vaccination at age 1 and 11 at 95/80% coverage compared to 50/50% coverage: net QALY's gained/lost according to time horizon. QALY's are discounted at 1.5%.



4.2.2 Impact of vaccination against CP assuming no exogenous boosting

All scenarios assuming no exogenous boosting are run with the current most likely vaccine price/dose in Belgium of €43.46, in case of bulk purchase.

4.2.2.1 Impact of 2-dose vaccination on annual number of CP (and HZ) infections when no boosting assumed

- Vaccination programs with high vaccine uptake result in a larger overall decrease in number of primary CP infections (Figure 67), HZ infections and in a smaller number of breakthrough CP infections, compared to vaccination programs with a lower uptake.
- Vaccinating at age 1 and 11 induces a smaller temporary increase in CP infections in 15-25 year olds, but a larger temporary increase in 5-14 and 25-59 year olds, compared to vaccinating at age 1 and 4 (Figure 68 and Figure 69).
- A vaccination program with vaccine uptake of 50%/50% (i.e. in both age groups) results in a higher annual number of CP infections in persons aged 15 and older compared to a situation without vaccination (Figure 70). This is not the case for vaccination programs with high uptake of the vaccine (e.g. see 2 high uptake scenarios in Figure 68 and Figure 69).

Figure 67: Number of primary CP infections over time for 3 different vaccination scenarios (no boosting assumed). Time point 0 represents the situation without vaccination.

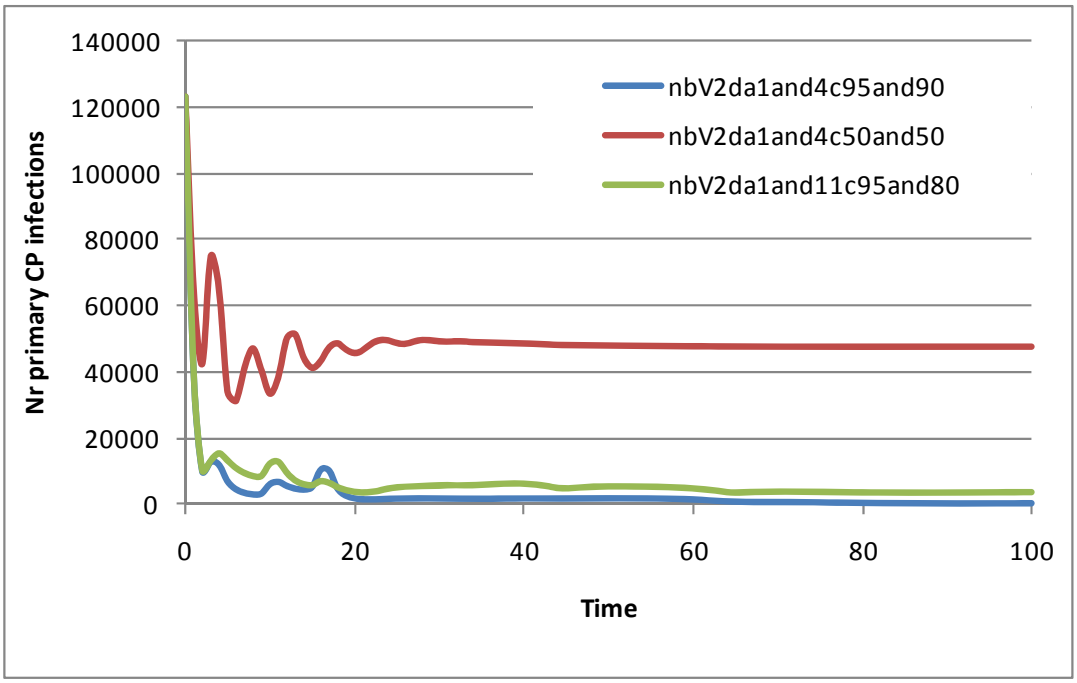


Figure 68: Scenario CP 2-dose vaccination at ages 1 and 4 years, at coverage 95% and 90%, no boosting assumed: Number of primary CP infections over time, by age group. Note that for clarity, x-axis starts from time point 2.

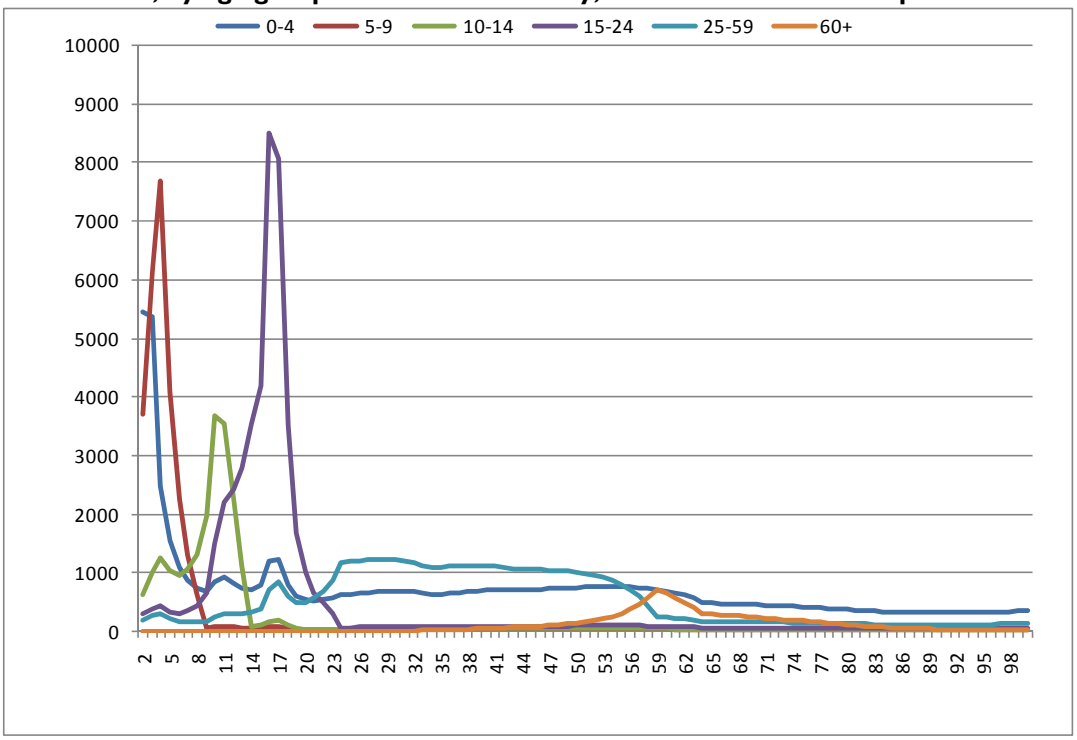


Figure 69: Scenario CP 2-dose vaccination at ages 1 and11 years, at coverage 95% and 80%, no boosting assumed: Number of primary CP infections over time, by age group. Note that for clarity, x-axis starts from time point 2.

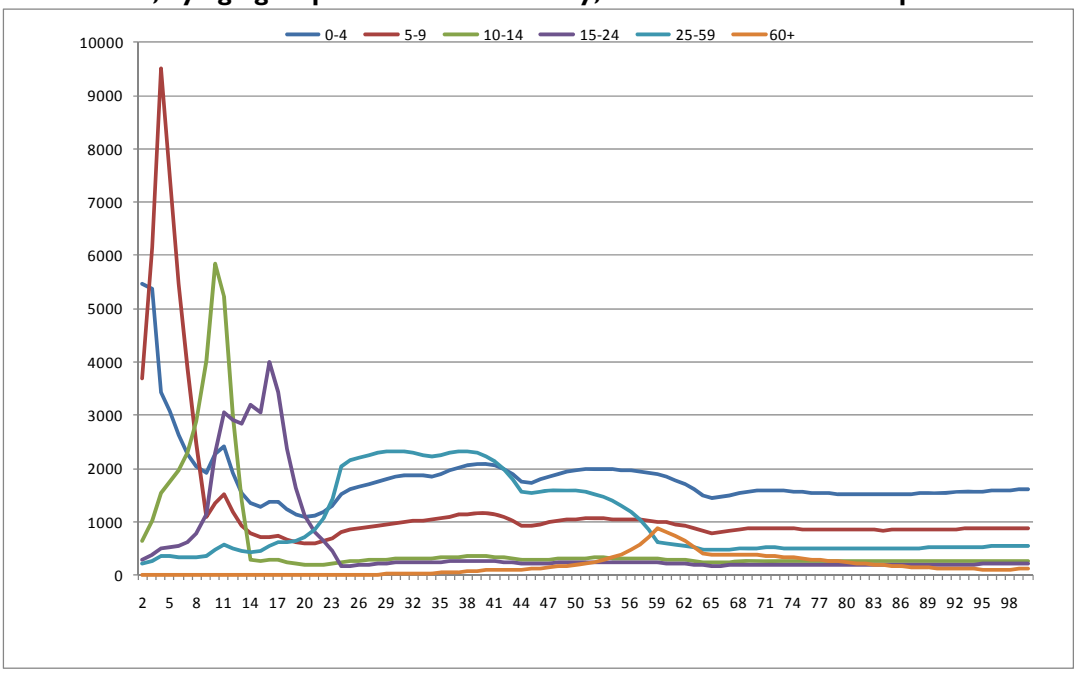
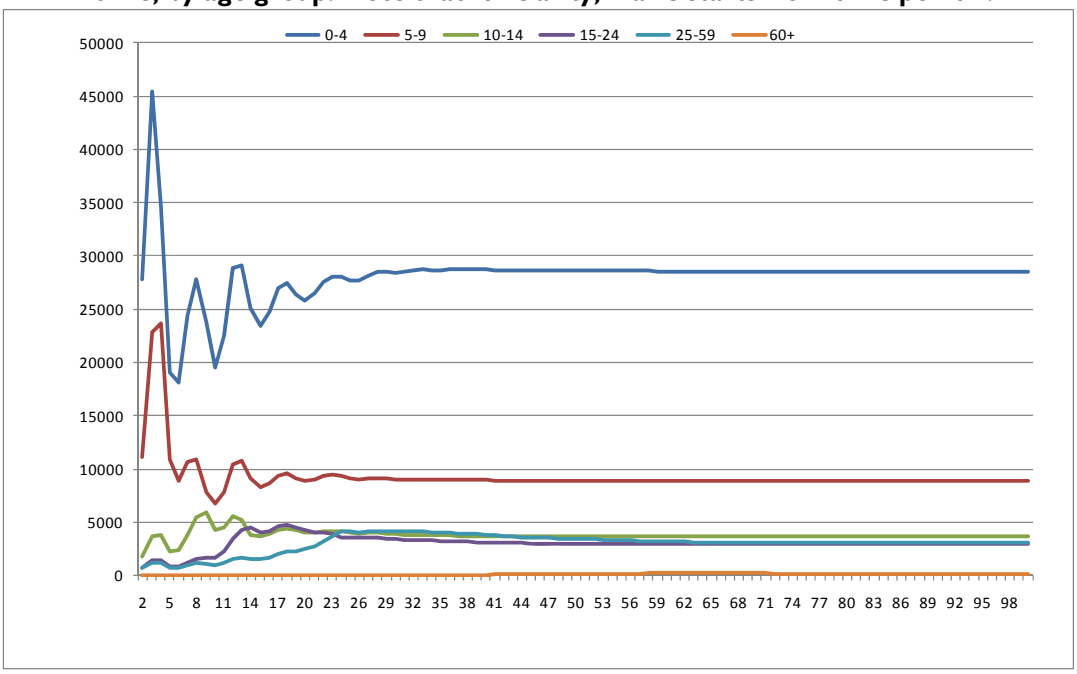


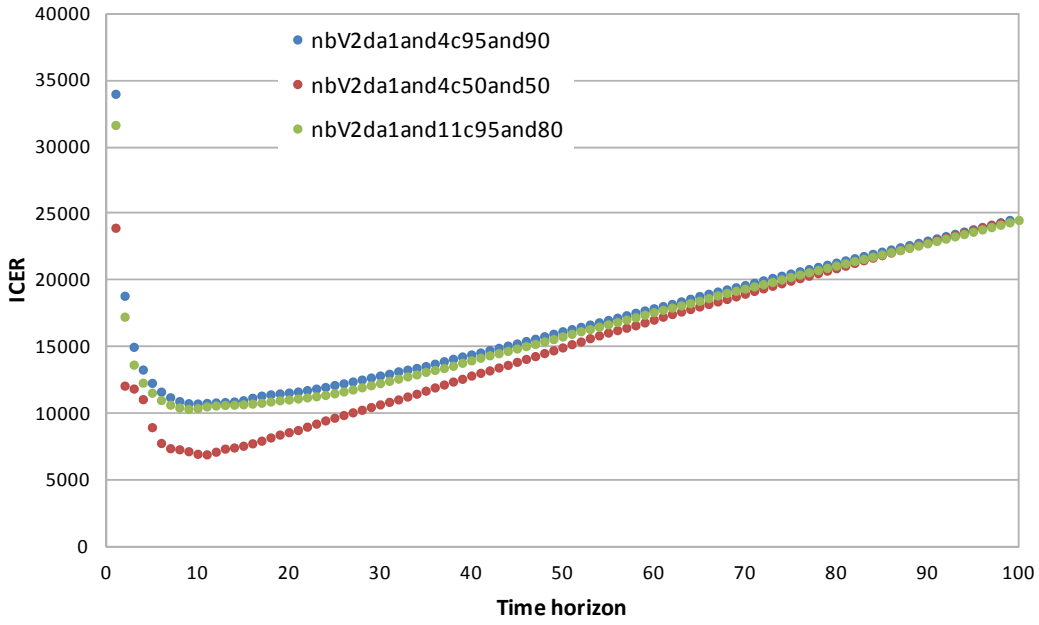
Figure 70: Scenario CP 2-dose vaccination at ages 1 and 4 years, at coverage 50% and 50%, no boosting assumed: Number of primary CP infections over time, by age group. Note that for clarity, x-axis starts from time point 2.



4.2.2.2 Cost-utility of 2-dose CP vaccination when no exogenous boosting assumed

- Under the assumptions used, all 2-dose vaccination programs against CP considered are cost-effective for many years after vaccination when only including the effect on CP disease (Figure 71). Taking into account the effect of CP vaccination on HZ disease, makes such 2 dose vaccination program even more cost-effective, with direct costs per QALY gained stabilizing around €10,000.
- Vaccination at age 1 and 11 (at 95% and 80%) is slightly more cost-effective than vaccination at 1 and 4 (at 95% and 90%). Also, vaccination at age 1 and 4 at lower coverage rates is found to be more cost-effective than vaccination at the same ages, but at higher coverage. This is because of the herd immunity effect: e.g. with a 2-dose vaccination program at coverage 50% and 50%, about half of the vaccination costs are incurred but substantially more than half the number of infections are avoided, in comparison to a 2-dose vaccination program at coverage of 95% and 90%.

Figure 71: Incremental direct cost per QALY gained for 3 different CP vaccination scenarios in Belgium, compared to no vaccination, over time. No boosting is assumed, and only the impact on CP disease is taken into account. Discount rate for costs 3%, for life years 1.5%.



5 DISCUSSION

5.1 VACCINATION AGAINST HZ

For several key variables, substantial uncertainty exists about which data source and/or model to use to estimate these variables. This uncertainty increases with increasing age of the cohort considered to be vaccinated, and has a major impact on HZ vaccination being cost-effective for Belgium, and at which ages. Under assumptions least in favour of vaccination, vaccination would be cost-effective (i.e. ICER <€30,000/QALY) at a vaccine price of €45/dose, for age cohorts 60-64. The vaccine price should drop below €1/dose, for vaccination to be cost-effective (i.e. ICER <€30,000/QALY) for all age cohorts 60 until (including) 85 combined.

Both our scenario analyses and the comparison of our results with other health economic evaluations of Zostavax® vaccination reveal some key factors to which the cost-effectiveness of Zostavax® vaccination (by age) is very sensitive:

- Estimated SOIS and loss in QoL due to HZ case by age

The age-specific QALY loss related to an HZ episode was found to be important in determining the cost-effectiveness of HZ vaccination in a range of studies (e.g. van Hoek et al[43]). Also, the estimated age-specific QALY loss differs substantially between different studies. Our estimate (based on Scott et al[34]) is higher than that of van Hoek et al[43] and Pellisier et al[64], but lower than what was estimated by Edmunds et al[95]. Also, van Hoek et al[43] estimated a steeper increase in QALY loss by age compared to the three other studies. These differences are due to the use of different data sources. van Hoek et al[43]'s estimate is based on data measured in a range of different populations, such as for instance PHN patients only, eligible persons for a clinical trial, and immunocompetent people only. The HZ-related QALY losses estimated by Pellissier et al[64] were based on data from the SPS trial[27], and the estimates from Edmunds et al[95] were based on a study using standard gambling techniques in 65-70 year olds. As the population in which HZ-related loss in QoL (and SOIS) is estimated should be representative for the population considered to be vaccinated, and since it was not feasible to set up a timely survey measuring QALY loss in the Belgian population, we decided to derive estimates only from studies that estimated QALY loss (and SOIS) in the general community. Also, our cost-utility analysis is the only one that estimated age-specific HZ-related loss in QoL (and costs) in function of age-specific HZ-related severity-of-illness (SOIS). Advantages of this approach are that 1) it allowed us to correct our survey in ambulatory HZ patients for possible bias towards patients with more severe disease, and 2) it allowed to assess the impact of efficacy against burden-of-illness (the primary endpoint of the Oxman et al[27] trial) (see further). However, our approach's major downside is that the only two studies that measured HZ-related SOIS in the general community by age, measured quite different SOIS averages, and that we are not able to explain this difference (for a detailed discussion, see p.31). Since there are only two, diverging prospective community based studies, and since one of them is a relatively small study[34], it is important to repeat this type of studies. Moreover, it would be useful if estimates for QALY loss for a complete HZ episode became available from the Drolet et al[46] study.

- Estimated waning of the vaccine, by age

There are many difficulties regarding the estimation of the waning of the HZ vaccine efficacy. Firstly, data on vaccine efficacy are only available up to 7 years after vaccination, but for CUA we want to make predictions up to about 50 years after vaccination. Secondly, HZ vaccines given to the persons included earliest in the SPS trial (and who were followed-up the longest), were not frozen (or frozen for a shorter time), and/or had higher dose potencies[96], and the effect of this on vaccine efficacy remains unclear. Thirdly, data on efficacy by age (in years instead of age groups) and year after vaccination combined are not public, nor available for independent analyses. Fourthly, waning immunity models for other vaccines can hardly be applied here, as this is a attenuated vaccine and most of the existing evidence is from inactivated vaccines.

In addition, this vaccine is not intended to prime the immune system but to boost previously acquired immunity. Therefore extrapolation from existing evidence on other vaccines is of little relevance. Nonetheless, various approaches to estimate HZ vaccine efficacy by age and year after vaccination have been done. Given the same data, these methods should result in similar estimates. Indeed, van Hoek et al[43] estimated vaccine take and waning simultaneously by fitting a mathematical model to the SPS trial data, while we estimated efficacy statistically. The resulting best fit of van Hoek et al (protection of 7.5 years for all ages), is similar to our estimate based on the exponential waning model[84]. Also, in both studies, the uncertainty surrounding the estimated duration of protection was very large and found to be influential for the cost-effectiveness of vaccination. Pellissier et al[64] used yet another approach and estimated no waning of efficacy. Even if we use the same approach as Pellissier et al[64] (exponential waning but assuming number of HZ cases having a binomial instead of a Poisson distribution), our best estimate is 7.7 years of protection[84]. It is noteworthy that vaccine efficacy is found to decrease with age at vaccination, which is likely to reflect immunosenescence. If one assumes little or no waning of vaccine efficacy, this means that a 75 year old would be better protected if vaccinated at age 60 rather than at age 74 (and, given no waning, one could even argue to vaccinate before age 60). It is however difficult to assess which of the approaches results in the most realistic estimates, because of the scarce publicly available data. The availability of more detailed data from the SPS trial would allow estimating efficacy by age and over time more accurately. Also, post-vaccination surveillance data from countries that have introduced the vaccine would be important to improve the estimates of duration of protection. Moreover, it would be useful to conduct more basic research on the vaccine induced immune response in elderly over time, in particular through attenuated vaccines. Also, it may be of use to investigate whether vaccinated people can still get HZ, and if so, what the burden of this "breakthrough HZ" is.

- Population that can benefit from the vaccine

Although the Zostavax® vaccine is only indicated for immunocompetent persons, only taking into account the effect of the vaccine for immunocompetent persons (as for instance done by van Hoek et al[43]) may underestimate the potential benefits of this vaccine. This is due to the fact that immunocompromised persons may be vaccinated before they converse to the immunocompromised status. However, it is unclear if they are still protected against HZ when they converse to the immunocompromised status. On the other hand, taking all the HZ burden into account, may lead to an overestimation of the effect of the vaccine. Our study and Pellissier et al[64] show the difference in cost-effectiveness of HZ vaccination between both scenario's, and hence the importance of studying more closely who possibly can benefit from the vaccine.

- Taking into account additional efficacy against BOI and/or PHN

BOI is a severity-by-duration measure of the total pain and discomfort associated with HZ in a population. Vaccine efficacy against BOI hence includes the decrease in number of HZ cases, as well as the duration and severity of HZ disease. Therefore cost per QALY gained becomes lower when BOI is accounted for, and this especially for older ages. However, the measure of BOI has been criticized, as it would tend to overestimate the efficacy[96]. Also, BOI is based on HZ-related SOIS, but it is not clear how accurate such SOIS can be measured: HZ-related SOIS as measured by Drolet et al[46] and Scott et al[34] differ substantially, despite a very comparable study population and methodology. Furthermore, it is not very clear how to determine the decrease in costs and QALY's associated with a decrease in BOI. Van Hoek et al[43] and Pellissier et al[64] assumed that the decrease in BOI was only associated with a reduced QALY loss over the first six months in vaccinees who developed HZ. We assumed it impacts both on incremental costs and QALY's, by modelling the average cost and QALY loss related to HZ as a function of the average SOIS by age. But even then, we do not take into account that BOI (and SOIS) are a combination of different variables (disease duration and severity), which may influence incremental costs and effects differently. For example, costs may be stronger related with the duration than with the severity of HZ disease.

PHN is defined in the SPS trial[27] as pain associated with HZ that was rated as 3 or more on a scale ranging from 0 to 10, persisting or appearing more than 90 days after the onset of rash. Other definitions for PHN are possible, but they all reflect some sort of cut-off value based on duration and severity of HZ disease. Hence the additional efficacy against PHN is accounted for by the additional efficacy against BOI. As such, it may be valuable to elaborate on how to measure duration and severity of HZ disease more accurately, rather than to use the non-standardised (artificial) definition of PHN.

- Age-specific estimated HZ burden

Our analyses show that the age at which vaccination is found to be most cost-effective depends on how some of the input parameters are modelled by age (e.g. how fast HZ-related SOIS increases with age). For several HZ burden parameters, van Hoek et al[43] estimated a faster increase with age compared to our study. Pellissier et al[64] estimated a higher proportion of HZ cases having PHN by age, and also a faster increase in HZ case fatality rate by age compared to our study. The different trends by age may be due to country-specific differences, but can also be due to modelling assumptions (e.g. how flexible the statistical models for fitting parameters by age are). Estimating how the HZ burden changes by age becomes increasingly more difficult for older ages, because the number of surviving elderly decreases rapidly with further increasing age. Indeed, our analyses show that the uncertainty around the HZ burden becomes increasingly larger for older ages.

An additional difficulty is related to the fact that HZ occurs in the elderly, and that it is more common in people with diminished cell mediated immunity. These people are more likely to have comorbidities, which makes it more difficult to assess which costs and QALY's are related to HZ, and could be prevented by HZ vaccination. This could (partially) explain the large variation in estimated costs for PHN cases between the different available cost-effectiveness studies. For instance, van Hoek et al[43] and Pellissier et al[64] respectively estimated the cost of a PHN case to be 4.5 and 6 times higher than the cost for a HZ case without PHN. Based on the NCSF survey, we estimated this cost only to be 1.6 times the cost of a HZ case without PHN. We assessed the HZ related costs by conducting a survey, specifically asking for all costs related to HZ. But respondents found it not always easy to distinguish between costs related to HZ or another disease. Alternatively, one could do a matched case-control study, assessing the incremental costs due to HZ indirectly when comparing a population with HZ with a similar population without HZ[97, 98]. One of the major difficulties of such an approach is however the choice of an appropriate control group.

- Antiviral medication

As we do not have information on a possible synergetic effect of the vaccine and the use of antiviral medication, and as we do not have sufficiently detailed information on the influence of antiviral medication on the SOIS, these possible effects have not been quantified in our CEA. However, through the collection of additional information via the GP sentinel service, we were able to verify that the proportion of herpes zoster patients receiving antiviral medication in Belgium is similar to the proportion observed in the SPS trial.

5.1.1 Comparison of our results with previous published CUA's.

At the moment of this writing, nine health economic evaluations of Zostavax vaccination are published[43, 64, 76, 92, 95, 99-102]. Six studies found Zostavax vaccination likely to be cost-effective at the assumed vaccine price, at all or some of the ages considered[43, 64, 92, 95, 99, 101]. Rothberg et al[76] however found vaccination to be quite expensive (although the cost-effectiveness of vaccinating 70-year-old women (US$43,650/QALY) is found to be attractive). Van Lier et al[102] found vaccination to be marginally cost-effective, even at the economical most attractive option (i.e. €21,716/QALY for vaccination at age 70). As our study, Hornberger et al[100] concluded that resolution of uncertainties about the average quality-of-life effects of acute zoster and the duration of vaccine efficacy is needed to better determine the cost-effectiveness of zoster vaccination in older adults. A reason why many of the other studies did not conclude so, is because only a selection of uncertainties was accounted for, and/or because the impact of different sources of uncertainty was not investigated

simultaneously (e.g. by doing multivariate scenario analyses or include them all in PSA). Note that only Annemans et al[92] and Pellissier et al[64] (two studies that declared conflicts of interest) report this does not change their conclusion of vaccinating being cost-effective for people aged 60 and older.

Also the age at which vaccination is (most) cost-effective, differs between the studies. Most studies found vaccination to be most cost-effective at around age 70. Only Pellissier et al[64] found, as in our study, vaccination to be most cost-effective at the youngest age considered. In all analyses, age-specific ICERs are very sensitive to the values of some key parameters. Possible explanations why we found in most scenario's vaccination to be more cost-effective for 60 year olds than for older people, and that this is in contrast with some of the other studies, are (most of them are already discussed before in more detail):

- For the scenarios least in favour of vaccination, vaccine efficacy was estimated to wane faster for older ages compared to younger ages. In previous published studies, waning was assumed to be independent of age.
- For several HZ burden parameters (e.g. HZ case fatality rate, HZ QALY loss), other studies estimated a faster increase with age compared to our study.
- PHN-related parameters: e.g. we estimated the cost of a PHN case not that much higher compared to the cost of a HZ case without PHN, in comparison with other studies.

5.1.2 Strengths and weaknesses of our CUA of HZ booster vaccination in elderly compared to previously published CUA's, with respect to:

Data sources used

Almost all of the input parameters for our CUA are estimated using Belgian data (with the exception of HZ-related SOIS and QALY loss, and vaccine efficacy). A thorough investigation of the representativeness of these data sources for the Belgian population was performed, and if necessary, a bias correction was done (e.g. for the NCSF survey in ambulatory HZ patients). However, this latter correction was based on studies performed in a non-Belgian population (Scott et al and Drolet et al), for which it is unclear how representative they are for the Belgian context (see further).

Scenario's ran

Unlike many other CUA's, we decided not to present a 'base case' scenario, because we did not want to choose randomly between different data sources, models or assumptions for which no evidence exists about which of them is the better one to use. This may not make the task of decision makers easier, because they will be forced to acknowledge uncertainty (as no single 'base case' value is presented). However, this is what we believe CUA aims to do: inform the decision maker on costs, effects and cost-effectiveness, and the uncertainty surrounding these variables. However, we acknowledge that also the scenario's most and least in favour of vaccination presented, are only two of many possible scenarios, and do not necessarily reflect the 'real' most and least in favour scenario's.

Our study and the study of Pellissier et al[64], are the only ones that explored the impact of the assumption on which population can benefit from the vaccine. I.e. we ran a scenario assuming only HZ episodes in immunocompetent persons can be avoided by introducing a vaccination program, because the Zostavax® vaccine is tested in, and recommended for immunocompetent persons only. Proportions of ambulatory and hospitalized HZ patients in immunocompetent persons (according to Oxman et al[27]'s exclusion criteria) are derived from surveys in the Belgian population, for 4 different age groups. Unfortunately, SOIS for HZ episodes in immunocompetent persons is derived from a non-Belgian source (Scott et al[34]) , whose definition of immunocompetence does not necessarily concur with ours. Also, it remains unclear which population will benefit from the vaccine when it is introduced: Will immunocompromised persons be vaccinated, and if so, will they be protected against HZ and how much? What happens when (vaccinated) immunocompetent people become immunocompromised? Therefore, the difference in cost-effectiveness resulting from assuming all HZ episodes

can be avoided through vaccination, as opposed to only the episodes in the immunocompetent persons, shows the importance of studying more closely who possibly can benefit from the vaccine, rather than that it quantifies the cost-effectiveness of HZ vaccination in two realistic populations.

In addition to univariate scenario analysis, we also did extensive multivariate scenario analyses. For our CUA, this was highly important. Indeed, based on univariate analysis one would conclude under the scenario most in favour of vaccination that HZ vaccination remains cost-effective no matter which input parameter is changed individually; and under the scenario least in favour of vaccination that HZ vaccination remains cost-ineffective no matter which input parameter is changed individually. However, our scenario analyses was mainly restricted to the influence of five uncertain input parameters, and explored the importance of age at vaccination, discount rate and vaccine price. Although we believe we have covered the most important input parameters, other currently ignored input parameters may also be important in determining the cost-effectiveness vaccination (e.g. gender has been found to be influential on cost-effectiveness of HZ vaccination[76]). Another drawback of our CUA is that no formal quantification of the importance of each input parameter or assumption for the cost-effectiveness of HZ vaccination could be done.

Parameter estimation

Estimation as a function of age: Age is an important covariate in determining HZ incidence. We estimated all but one (proportion of HZ hospitalized patients not visiting a GP) of the input parameters as a function of age. For most of them a flexible statistical model was fitted to the data with age as a continuous covariate, rather than estimates for several discrete age groups. Disadvantage of this approach is that for such statistical models it becomes troublesome (or even impossible) to quantify parameter uncertainty, and hence we could not do this within the time frame of the current CUA. However, we believe obtaining accurate age-specific mean estimates to be more important than being able to quantify parameter uncertainty, given that data source uncertainty dominates parameter uncertainty. Therefore, we also decided not to perform a probabilistic sensitivity analysis (PSA). PSA would only take into account parameter uncertainty that could be quantified and consequently would not give a complete picture of all the parameter uncertainty involved.

Estimation of vaccine efficacy as a function of age and time since vaccination: We fitted statistical models to the available data to estimate vaccine efficacy by age and time since vaccination. But because of the lack of publicly available data on vaccine efficacy over age and time together, the types of statistical models that could be fitted to the data were limited, and no single best-fitting model could be identified. Hence we show the impact of the different models on the results of the CUA, but of course the problem remains that we do not know how far or close these models are from what happens in reality. This problem is true also for other approaches of estimating vaccine efficacy (e.g. based on mathematical models (van Hoek et al[43])) and can only be solved when data on the efficacy of the vaccine by age and time since vaccination become available (and when the underlying processes of how the vaccine works are better understood).

Estimation of costs and QALY loss as a function of SOIS: This is the first study that estimated HZ-related costs and QALY loss as a function of SOIS, to use as input in CUA. The advantages of this approach are that 1) it allowed us to correct our survey in ambulatory HZ patients for possible bias towards patients with more severe disease, and 2) it allowed to assess the impact of efficacy against burden-of-illness (the primary endpoint of the Oxman et al[27] trial).

Our estimated HZ-related QALY loss however is likely an overestimation, as we assumed people without HZ to have utility scores of 1. This overestimation is larger for older ages, as non-disease specific utility score is decreasing with increasing age (Kind et al 1998). However, if we would use non-disease specific utility scores for people without HZ instead of 1, our conclusion that HZ vaccination is likely more cost-effective at age 60-65 compared to older ages, would only become stronger.

As the population in which HZ-related loss in QoL and SOIS is estimated should be representative for the population considered to be vaccinated, and since it was not feasible to set up a timely survey measuring QALY loss and SOIS prospectively in the Belgian population, we decided to derive estimates only from studies that estimated QALY loss and SOIS in the general community, in contrast with previous published CUA's. However, the major downside of this approach is that the only two studies that measured HZ-related QALY loss and SOIS in the general community by age, measured quite different SOIS averages, and that we are not able to explain this difference. Hence, it is not possible to assess which one of the two studies (if any) is most representative for the Belgian population. Note that the Scott et al[34] study followed a quite small population (n=65), especially given the large variation in SOIS between individuals. In view of this, it could be more correct to give a weight according to sample size to each of the studies, instead of giving them equal weight.

5.1.3 General conclusion

A large prospective study measuring (SOIS and) QALY loss would be very useful to improve analyses on this subject. Furthermore, existing information from the vaccine manufacturer lacks transparency: both on efficacy over time and age, and which people can possibly benefit from the vaccine.

Therefore, we can conclude now only that if the vaccine price per dose drops sufficiently (and becomes a small fraction of currently available prices), vaccination of older adults against HZ is likely to be cost-effective.

5.2 VACCINATION AGAINST CP (AND HZ)

The exogenous boosting hypothesis and the choice of time horizon completely determine if universal CP vaccination is possibly cost-effective or not. If the boosting hypothesis is true, the annual number of HZ infections is expected to increase significantly in the first 30 to 50 years after introduction of a chickenpox vaccination program in Belgium. The role of a booster vaccination dose for adults aged 60 to amend this problem created by chickenpox vaccination is limited. As this increase in HZ cases results in a net loss in QALYs for many years after vaccine introduction, it would not be effective, nor cost-effective, to target all children with a VZV vaccine (nor with the combined MMR-V vaccine). However, if the boosting hypothesis is not true, or if costs and QALY's are considered over a sufficiently long period of time, universal 2-dose vaccination against CP in Belgium would be cost-effective at a vaccine price of €43.46/dose.

With the exogenous boosting hypothesis one assumes that an "effective" contact (in the current analysis defined as contacts which involve touching and last longer than 15 minutes) with a person suffering from CP, boosts the immune system of a person who once was infected by CP, so that his/her probability to get HZ decreases. Currently there is however only indirect evidence that supports this hypothesis[23-27] (see also background on p.4). Also, although children in the US have been vaccinated against CP for more than 10 years, there is still conflicting evidence to this matter[103-106]. This may be due to various reasons, including (1) vaccine uptake was low over the first 5 years in the US, and differed substantially between different US states; (2) the US used a single dose of VZV vaccine for the first 11 years of the program; (3) due to the difficulties in making a clear case definition, zoster surveillance suffers from inconsistent reporting, and the reported zoster incidence may have been rising prior to the introduction of VZV vaccine. However, recent publications on the situation in Australia[107-109] point at an increase in HZ incidence after a nationally funded CP programme was agreed upon in 2005. However, it remains difficult to associate this increase directly to the introduction of that program.

A question a decision maker should ask him/herself at this stage, is whether s/he would decide to introduce a vaccination program which reduces substantially the occurrence of one disease (CP), but may increase the occurrence of another disease (HZ). If the answer to this question is no, universal CP vaccination in Belgium should currently not be recommended until/unless:

- More accurate information on the this hypothesis of exogenous boosting is available. Note that as long as this hypothesis holds (even if the duration of protection is short, see Figure 57), the initial increase in HZ infections following CP vaccination is expected to occur.
- As the increase in HZ infections caused by CP vaccination occurs for all adults, giving adults of a large range of ages a booster vaccination dose at high levels of coverage might alter this increase. Such a booster dose may need to be repeated, as it may not provide lifelong protection against HZ. However, it is unlikely that such strategy, even if it is proven to alter sufficiently the initial increase in HZ infections following CP vaccination, is found to be cost-effective, and is believed to be feasible to put into practice.

Alternatively, the decision maker may want to consider also the costs, life years and QALY's lost related to CP and HZ disease, and be interested in the net cost and net benefit of a CP (and HZ) vaccination program. If the exogenous boosting hypothesis is true, there will be a net loss in QALYs for many years after vaccine introduction, although the increase in HZ-related costs and life years lost is altered by a higher amount of costs saved and life years gained due to the prevention of CP infections. Hence, it would not be effective, nor cost-effective, to target all children with a VZV vaccine. This depends of course on how the average loss in QoL for a CP case is estimated relatively to the average loss in QoL for a HZ case. Note however that we used rather high disutility weights for CP compared to other studies[48, 50], and relatively low disutility weights for HZ (based on the SOIS obtained from Scott et al[34]), but still obtain net losses in QALYs for many years after the start of CP vaccination, and even if this is combined with HZ vaccination. So for many decades following the start of the program, it would not be cost-effective. However, if the population at the start of the simulation is nearly completely replaced by a (partially, given the vaccine uptake) vaccinated population more than about 80 years later, then the program becomes cost-effective. Hence, the critical question at this stage becomes, how long in the future should we take costs and benefits into account, and at which discount rate? Clearly, over a period of 80 years, huge changes in society are likely to happen, and profound technological progress, with hardly imaginable changes to medical practice are expected to occur. Simulations over such a long time frame are therefore likely to be very inaccurate. On the other hand, if the exogenous boosting theory is not true, universal 2-dose vaccination of children against CP is found to be cost-effective at current vaccine price levels. Although strictly not the most cost-effective strategy given the point estimates shown in this section, a 2-dose vaccination program at age 1 and 4 at coverage 95% and 90% results in the highest decrease in number of both CP and HZ cases (and hence the highest decrease in treatment costs and QALY gains). Furthermore, in contrast with programs with lower coverage rates (50% or 70%), no increase in the annual number of CP infections in persons aged 15 and older is expected after vaccination.

If for some reason, e.g. vaccination reimbursed only by some health insurers, vaccine uptake levels reach about 50%/50% compared with 95/80-90% as in a program, the total annual number of cases of chickenpox in adults will be higher, the increase in HZ cases for the first 35 years will be substantially lower, but still, up to 70 years after vaccination, a net loss in accumulated QALY's is expected.

Quadrivalent combination vaccine- Since March 2009 (http://www.cbip.be/Folia/index.cfm?FoliaWelk=F36F04C&keyword=Priorix tetra, latest accessed 30/11/2010), a quadrivalent MMR-V vaccine is on the market in Belgium: Priorix-Tetra™ which costs €63.93 (http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_1.cfm, latest accessed 30/11/2010). Although no formal cost-utility analysis was done considering this combined vaccine, the same conclusion can be drawn as for the single CP vaccine, i.e. the exogenous boosting hypothesis completely determines if universal CP vaccination is possibly cost-effective or not. Furthermore, it was found that children vaccinated with a first dose of the combined vaccine Priorix-Tetra™ show more frequently high fever, compared to children vaccinated with Priorix™ and the single CP vaccine Varilrix™ separately (such increase was found for incidence of fever ≥39°C[110], and fever≥38°C[111]).

Note that a an advantage of such combination vaccine could be that, when introduced, it may reach higher coverage rates compared to when adding an additional single varicella vaccine to the already busy vaccination scheme.

Is there then no cost-effective use of the VZV vaccine? As shown first by Beutels et al[112], for the health care system targeted vaccination of susceptible pre-adolescents at the age of 11 years would be the most certain cost-effective way of using this vaccine in a routine manner. Over the last 15 years this was confirmed and updated by economic evaluations in various countries[51, 91, 113-115], including in Belgium[116, 117].

While this type of analysis was not the subject of the current research report, it is likely that the results of a re-analysis would confirm that targeted vaccination of susceptible pre-adolescents would be a cost-effective way of spending scarce recourses in health care. The uncertainty with this approach is low compared to the other options considered in this report due to the fact that such a targeted intervention would have a negligible impact on the transmission of VZV in the population and therefore no impact on the incidence of herpes zoster. It would prevent VZV in those few pre-adolescents at age 11 years (about 5%) with a negative history of chickenpox. An influential factor for this approach is the negative predictive value of a negative or uncertain history of chickenpox. This was documented at about 11% in Flanders with the aid of parents[17] and at 23.6% to 74% in various other countries (reviewed in Thiry et al[118]). The reasons why this option has not been put into practice are twofold: (1) the impact on chickenpox at the population level is very marginal and public health advisors do not feel this is relevant for health policy; (2) there are practical difficulties with putting this option into practice related to the required two stage implementation approach: verifying whether the child is negative or uncertain about their varicella history and then vaccinating those who indicate they are. Yet we know that the case-fatality ratio increases steeply with age after age 15 years (see table 8)and we noted also upon inspection of the death records in Flanders for the period 1998-2007, that 4 likely attributable chickenpox deaths occurred in children aged 11 years or younger, and6 such deaths occurred at a later age (all but one after age 59 years).

Additionally, there is little discussion that ad-hoc vaccination of adults with a known (serology-based) negative history of varicella, particularly women at childbearing age, pediatricians and school teachers, is very likely to be cost-effective[118, 119].

5.2.1 Strengths and weaknesses of our CUA of VZV vaccination in children (and booster in adults) compared to previously published CUA's

Note that the strengths and weakness with respect to HZ-related parameters are extensively discussed above.

Data sources used

- As for HZ, almost all the parameters related to CP health care use, costs and QALY loss, are estimated using Belgian data (with the exception of the age-specific CP case fatality rate and burden of breakthrough CP cases). A strength of our CUA compared to previous ones, is that a survey was setup specifically in Belgium to measure CP-related loss in QoL in children, with and without medical care. Unfortunately, the study did not cover older children (>3 years of age) and children hospitalized for CP.
- Epidemiological parameters and estimates for take and waning of CP vaccine and HZ booster vaccine were estimated using Belgian data were possible (age-specific HZ reactivation rate, force of infection and contact matrix (see below)), or derived from the literature (van Hoek et al[66], Brisson et al[71] and Brisson and Edmunds[91]).

Model

An already extensively studied and improved dynamic model was used (van Hoek et al[66]), allowing detailed exploration of age-specific VZV disease transmission dynamics. A minor restriction of using this model, is that some of the uncertainties shown to be important in our separate CUA for HZ vaccination, could not be taken into account (e.g. avoiding HZ episodes in immunocompetent persons only).

Parameter estimation

Van Effelterre et al[32] showed that the choice of matrix (amongst the Anderson & May[94] configurations) can be very influential for dynamic models of VZV transmission. Indeed, the uncertainty surrounding the transmission matrix was found to be highly important for the cost-effectiveness of VZV vaccination in the UK (explaining about 29% of uncertainty in incremental costs and QALY's[120]). We did not integrate the impact of uncertainty regarding the choice of age-specific mixing patterns as part of the current analysis. However, in separate statistical and mathematical modelling studies, Ogunjimi et al[31] and Goeyvaerts et al[90] have shown (using different methods) that with social contacts which involve touching and with an accumulated contact time of more than 15 minutes per contact-day, better fits can be obtained to seroprevalence data (amongst a range of countries, including Belgium) than using previous standard approaches (using simplified mixing matrices as proposed in Anderson & May[94]) or other definitions of contact data collected in large country-specific surveys[29, 30].

No probabilistic sensitivity analysis was performed as not all parameter uncertainty could be quantified (see before), and also no formal quantification of the most influential parameters was done. However, the latter was done for the CUA of VZV vaccination in England&Wales, a CUA using the same dynamic model. This analysis revealed that the uncertainty surrounding the epidemiological parameters influenced the outcome of the CUA much more than the uncertaintyin cost- and QALY loss parameters. Particularly, for the base case scenario presented by van Hoek et al[121], uncertainty surrounding the estimates for duration of boosting and HZ reactivation rate for varicella vaccinees explained 62% and 47% of the uncertainty in incremental costs and QALY's gained, respectively, whereas the transmission matrix explained another 29%[120]. Although this analysis cannot be directly compared with our CUA, it confirms that indeed the duration of boosting is a crucial parameter for the outcome of the CUA.

6 APPENDICES

APPENDIX I QUESTIONNAIRE NCSF SURVEY

APPENDIX I HOSPITALISED

VRAGENLIJST WINDPOKKEN (varicella)

INLEIDING

De Christelijke Mutualiteit voert momenteel een onderzoek uit naar de gezondheidsgevolgen van een windpokkeninfectie en naar de kosten daarvan.
Om hier een goed beeld van te krijgen voeren we momenteel een aantal interviews uit bij mensen die een windpokkeninfectie doormaakten of waarvan hun kind een dergelijke infectie doormaakte. Daarom willen we ook graag uw verhaal horen.

Dit gesprek zal echter geen enkel gevolg hebben voor de terugbetaling en is ook geen controle.

ALGEMENE OMSCHRIJVING

Vermeld het antwoord bij iedere vraag op het invulblad (tab 1 van EXCEL-formulier).

1. Wat is uw band met de persoon die de windpokken heeft gehad?
(omcirkel het juiste antwoord)

1: ikzelf heb de windpokken gehad
2: moeder van het kind
3: vader van het kind
4: voogd van het kind
5: partner
6: Andere (bv. grootouder)

2. Hoeveel dagen heeft u / uw kind ziek gedrag vertoond ten gevolge van windpokken?
(Vul het aantal dagen in)

…… dagen

3. Heeft u / uw kind tijdens de windpokken nog een andere ziekte doorgemaakt (bijvoorbeeld: asthma, diabetes) ?

1: ja (indien ja, ga naar vraag 4)
2: neen (indien neen, ga naar vraag 5)

4. Om welke ziekte ging het?
(noteer de ziekte die de persoon vermeldt)

…….

CP PATIENTS (DUTCH)

1. Heeft u / uw kind blijvende littekens ten gevolge van windpokken?

1: ja
2: neen

2. Wat was de reden van opname in het ziekenhuis?
……
……

OVERZICHT KOSTEN

We zouden graag een overzicht maken van alle kosten waar u beroep op heeft gedaan omwille van de windpokken. Het kan hier zowel gaan om medische kosten (zoals doktersbezoeken, medicatiegebruik) als om niet-medische of persoonlijke kosten (zoals vervoer, oppas zieke kinderen, klein verlet op het werk). Let wel op dat u in uw overzicht enkel die zaken vermeldt die een gevolg waren van de windpokken. Eventuele dokterconsultaties of hospitalisaties die met andere aandoeningen te maken hadden, mogen we niet opnemen in dit overzicht.

MEDISCHE KOSTEN

Vul enkel de vragen in waarvoor kosten zijn gemaakt op het invulblad (tab 2 van EXCEL-formulier).
Van ieder van deze vragen wordt het aantal eenheden, de eigen bijdrage, de RIZIV-bijdrage en/of de totale kost gevraagd.

Vraag nr.		Eenheid
	MEDISCHE KOSTEN	
	Consultatie huisarts:	
7.	- Raadpleging op kabinet	Aantal
8.	- Huisbezoek	Aantal
	Consultatie specialist	
9.	- pediater	Aantal
10.	- huidspecialist	Aantal
11.	- andere specialist	Aantal
12.	Consultaties overige gezondheidsberoepen ambulant (zoals bv. verpleegkundige)	Aantal
13.	Telefonische consultaties met een arts	Aantal
14.	Raadpleging spoedgevallen (zonder hospitalisatie)	Aantal
15.	Hospitalisatie	Aantal dagen
16.	Ambulante technische onderzoeken (zoals bv. aanvragen labo)	Aantal aanvragen
17.	Terugbetaalde ambulante medicatie	Aantal verpakkingen
18.	Terugbetaalde ambulante verzorgingsproducten (zoals bv. zalven)	Aantal verpakkingen

NIET MEDISCHE OF PERSOONLIJKE KOSTEN

Vul enkel de vragen in waarvoor kosten zijn gemaakt op het invulblad (tab 1 van EXCEL-formulier).

Vraag nr.		
	NIET-MEDISCHE OF PERSOONLIJKE KOSTEN	
19.	Transport van/naar de dokter, hospitaal, … (met auto, bus, taxi, …)	1: minder dan €20 2: tussen €20 en €50 3: meer dan €50
20.	Niet terugbetaalde ambulante verzorgingsproducten (zoals bv. zalven)	1: minder dan €20 2: tussen €20 en €50 3: meer dan €50
21.	Niet terugbetaalde ambulante medicatie (zoals bv. Aciclovir)	1: minder dan €20 2: tussen €20 en €50 3: meer dan €50
22.	Betaalde hulpverlening aan huis (extra hulp omwille van windpokken van bv. betaalde oppas)	Kostprijs in het totaal
23.	Aantal dagen dat iemand anders (bv. ouder van het zieke kind, echtgenoot van de zieke volwassene) niet kon gaan werken (ook halve dagen)	Aantal dagen (nauwkeurigheid halve dag)
24.	Enkel indien iemand anders een aantal dagen niet kon gaan werken: In welk arbeidsregime werkt deze persoon? *(Slechts 1 enkel antwoord mogelijk – geef meest relevante)*	1: geen 2: arbeider 3: bediende 4: zelfstandige 5: niet gekend
25.	**ENKEL VOOR VOLWASSEN PATIËNTEN !!!** Aantal dagen dat u niet bent gaan werken omdat u windpokken had (ook halve dagen)	Aantal dagen (nauwkeurigheid halve dag)
26.	**ENKEL VOOR VOLWASSEN PATIËNTEN !!!** Enkel indien u een aantal dagen niet bent gaan werken: In welk arbeidsregime werkt u? *(Slechts 1 enkel antwoord mogelijk – geef meest relevante)*	1: geen 2: arbeider 3: bediende 4: zelfstandige 5: niet gekend

OPLEIDING

Vermeld het antwoord op het invulblad (tab 1 van EXCEL-formulier).

27. Wat is het hoogste opleidingsniveau van uw gezin?
(Slechts één enkel antwoord mogelijk – Omcirkel het antwoord)

1: geen diploma
2: Basisonderwijs (lagere school)
3: Beroepsonderwijs
4: technisch onderwijs

Hartelijk dank voor uw medewerking!

APPENDIX 1 HOSPITALISED CP PATIENTS (FRENCH)

QUESTIONNAIRE varicelle

INTRODUCTION

La Mutualité chrétienne mène actuellement une enquête concernant les conséquences sur la santé de la varicelle et des coûts engendrés par cette infection.
Afin de pouvoir dresser un tableau aussi correct que possible, nous réalisons actuellement un certain nombre d'interviews auprès de personnes qui ont eu la varicelle elles-mêmes ou leur enfant a eu une telle infection. C'est pourquoi, nous aimerions entendre votre récit à ce sujet.

Cet entretien n'aura toutefois aucune conséquence sur le remboursement et n'est en aucun cas un contrôle.

DESCRIPTION GENERALE

Pour chaque question, mentionnez la réponse sur le formulaire à compléter (onglet 1 du formulaire EXCEL).

1. Quel est votre lien avec la personne qui a eu la varicelle ?
   (entourez la réponse exacte)

   1: j'ai eu moi-même la varicelle
   2: mère de l'enfant
   3: père de l'enfant
   4: tuteur de l'enfant
   5: conjoint
   6: autres (ex. grands-parents)

2. Combien de jours avez-vous été malade / votre enfant a-t-il été malade suite à la varicelle ?
   (complétez le nombre de jours)

   …… jours

3. Pendant la varicelle, avez-vous / votre enfant a-t-il eu une autre maladie (par exemple: asthme, diabète) ?

   1: oui (si oui, passez à la question 4)
   2: non (si non, passez à la question 5)

4. De quelle maladie s'agissait-il ?
   (notez la maladie mentionnée par la personne)

   ……

1. Avez-vous / votre enfant a-t-il des cicatrices permanentes suite à la varicelle ?

   1: oui
   2: non

2. Pour quelles raisons y a-t-il eu une hospitalisation ?
   ……
   ……

APERCU DES COUTS

Nous aimerions dresser un inventaire de tous les coûts engendrés par la varicelle. Il peut s'agir tant de coûts médicaux (tels que visites de médecin, médicaments) que de coûts non médicaux ou personnels (tels que transport, garde pour enfants malades, absence au travail). Attention : dans votre aperçu, vous ne devez mentionner que les éléments qui ont un rapport direct avec la varicelle.
Les consultations de médecin ou hospitalisations éventuelles relatives à d'autres affections ne doivent pas être indiquées dans cet aperçu.

COUTS MEDICAUX

Complétez uniquement les questions pour lesquelles il y a eu des coûts mentionnés sur le formulaire de réponse (onglet 2 du formulaire EXCEL).
Pour chacune de ces questions, il y a lieu de compléter le nombre d'unités, la quote-part personnelle, l'intervention de l'INAMI et/ou le coût total.

Question Nr		Unité
	COUTS MEDICAUX	
	Consultation généraliste:	
7.	- Consultation au cabinet	Nombre
8.	- Visite à domicile	Nombre
	Consultation spécialiste	
9.	- pédiatre	Nombre
10.	- dermatologue	Nombre
11.	- autre spécialiste	Nombre
12.	Consultations autres professionnels de la santé ambulatoires (ex. infirmiers)	Nombre
13.	Contacts téléphoniques avec un médecin concernant cette infection	Nombre
14.	Consultations urgences (sans hospitalisation)	Nombre
15.	Hospitalisation	Nombre de jours
16.	Examens techniques ambulatoires (ex. demandes labo)	Nombre de demandes
17.	Médicaments ambulatoires remboursés	Nombre de conditionnements
18.	Produits de soins remboursés ambulatoires (ex: pommades)	Nombre de conditionnements

COUTS NON-MEDICAUX OU PERSONNELS

Complétez uniquement les questions pour lesquelles il y a eu des coûts mentionnés sur le formulaire de réponse (onglet 1 du formulaire EXCEL).

Question nr.		
	COUTS NON-MEDICAUX OU PERSONNELS	
19.	Transport vers le médecin, l'hôpital… (en voiture, bus, taxi, …)	1: moins de 20€ 2: entre 20 et 50 € 3: plus de 50 €
20.	Produits de soins ambulatoires non remboursés (ex. pommades)	1: moins de 20€ 2: entre 20 et 50 € 3: plus de 50 €
21.	Médicaments ambulatoires non remboursés (ex. Aciclovir)	1: moins de 20€ 2: entre 20 et 50 € 3: plus de 50 €
22.	Soins payés à domicile (aide supplémentaire en raison de la varicelle, p.ex. garde d'enfants)	Coût dans le total
23.	Nombre de jours qu'une autre personne (ex. parent de l'enfant malade, conjoint de l'adulte malade) n'a pas pu aller travailler (y compris les demi-jours).	Nombre de jours (au demi jour près)
24.	Uniquement si quelqu'un a eu une absence au travail: quel est le régime de travail de cette personne? *(Une seule réponse possible - indiquez la plus pertinente)*	1: aucun - 2: ouvrier - 3: employé - 4: indépendant - 5: pas connu
25.	**UNIQUEMENT POUR LES PATIENTS ADULTES !!!** Nombre de jours d'absence au travail en raison du varicelle (également demi-jours)	Nombre de jours (au demi jour près)
26.	**UNIQUEMENT POUR LES PATIENTS ADULTES !!!** Uniquement si vous n'avez pas été travailler pendant un certain nombre de jours: quel est votre régime de travail? *(Une seule réponse possible - indiquez la plus pertinente)*	1: aucun - 2: ouvrier - 3: employé - 4: indépendant - 5: pas connu

FORMATION

Mentionnez la réponse sur le formulaire de réponse (onglet 1 du formulaire EXCEL).

27. Quel est le niveau de formation le plus élevé dans votre ménage ?
(Une seule réponse possible – Entourez la réponse)

1: pas de diplôme
2: enseignement primaire
3: enseignement professionnel
4: enseignement technique
5: enseignement secondaire général
6: enseignement secondaire (école supérieure ou université)

Grand merci pour votre collaboration!

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4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
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12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
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16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
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19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
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23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
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